PROTOCOL: SHP643-101

TITLE:	A Phase 1, Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Pharmacodynamics of a Single Dose of Lanadelumab Administered Subcutaneously in Healthy Adult Japanese Subjects and Matched Healthy Adult Caucasian Subjects
DRUG:	SHP643, lanadelumab (formerly DX-2930)
IND:	116647
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Dyax Corp. (an indirect and wholly-owned subsidiary of Shire plc) 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	PPD , MD West Coast Clinical Trials 5630 West Cerritos Avenue Cypress, CA 90630 USA
PROTOCOL HISTORY:	Original Protocol: 27 Nov 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shi PPD

Signature:	**Date:** PPD
PPD PPD	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP643-101.

Title: A Phase 1, Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Pharmacodynamics of a Single Dose of Lanadelumab Administered Subcutaneously in Healthy Adult Japanese Subjects and Matched Healthy Adult Caucasian Subjects

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by fax or e-mail using the details below.

E-mail: PPD

For protocol- or safety-related issues, the investigator must contact the Shire Medical Monitor:

PPD

Telephone: PPD (business hours)
PPD (24-hour coverage)

ADDITIONAL CONTACT INFORMATION

In case of any other issues, including non-safety-related issues or if the medical monitor is unable to be reached, the investigator must contact the Shire Study Manager:

PPD

Telephone: PPD (24-hour coverage)
PPD
E-mail: PPD

If unavailable, please contact:

PPD
PPD

Telephone: PPD (24-hour coverage)
PPD
E-mail: PPD

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Shire, Lexington, MA (USA)

PPD

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

λ_z	Terminal elimination rate constant
%CV	Percent coefficient of variation
AE	Adverse Event
ADA	Anti-drug antibody
aPTT	Activated partial thromboplastin time
$AUC_{0\text{-last}}$	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
β-hCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
CRA	Clinical Research Associate
CRC	Clinical Research Center
CRF	Case Report Form
cHMWK	Cleaved High Molecular Weight Kininogen
C_{max}	Maximum Observed Plasma Drug Concentration
C1-INH	C1 Inhibitor
CHO	Chinese Hamster Ovary
CL/F	Apparent Clearance
CRO	Contract Research Organization
CV%	Coefficient of Variation
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HAE	Hereditary Angioedema
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IgG1	Immunoglobulin G Subclass 1
IRB	Institutional Review Board
IRT	Interactive Response Technology
Ki	Inhibition Constant
MHLW	Ministry of Health, Labor and Welfare
LLOQ	Lower limit of Quantification
Mg	Milligram
mL	Milliliter
mmHG	Millimeters Mercury
PD	Pharmacodynamic
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Time elapsed from P wave to R wave in an electrocardiogram
PT	Prothrombin Time
QRS	Measure of time for the 3 main deflections in an electrocardiogram
QT	Measure of time between the start of the Q wave and the end of the T wave in an electrocardiogram
QTcB	Measure of time between the start of the Q wave and the end of the T wave using Bazett's formula in an electrocardiogram
QTcF	Measure of time between the start of the Q wave and the end of the T wave using Fridericia's formula in an electrocardiogram
RR	The time between heart beats in an electrocardiogram
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
$t_{½}$	Terminal half-life
US	United States
$Vd_{z/F}$	Apparent Volume of Distribution

STUDY SYNOPSIS

Protocol number: SHP643-101	**Drug:** Lanadelumab
Title of the study: A Phase 1, Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Pharmacodynamics of a Single Dose of Lanadelumab Administered Subcutaneously in Healthy Adult Japanese Subjects and Matched Healthy Adult Caucasian Subjects	
Number of subjects (total and for each treatment arm): A total of 32 healthy adult, male and/or female subjects will be enrolled into the study, comprising 16 subjects of Japanese descent and 16 matched, non-Hispanic, Caucasian subjects. Assuming a 25% dropout rate, approximately 24 subjects (12 from each race/ethnicity) are expected to complete the study. Study subjects who withdraw or discontinue early may be replaced at the discretion of the sponsor. Non-Hispanic, Caucasian subjects will be matched to subjects of Japanese descent based on sex (1:1 male: male, female: female), age (±5 years), and body mass index (±15%). • The subjects of Japanese descent will receive one single 300mg subcutaneous (SC) dose of lanadelumab. • Matched, non-Hispanic, Caucasian subjects will receive one single 300mg SC dose of lanadelumab.	
Investigator(s): PPD , MD	
Site(s) and Region(s): West Coast Clinical Trials 5630 Cerritos Ave. Cypress, CA 09630	
Study period (planned): 2018	**Clinical phase:** 1
Objectives: **Primary:** To evaluate the pharmacokinetic (PK) properties of lanadelumab administered as a single SC dose of 300 mg in healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy volunteer subjects. **Secondary:** To assess the safety and tolerability of lanadelumab administered as a single SC dose of 300 mg to healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy volunteer subjects. Endpoints corresponding to the primary and secondary objectives are defined in the endpoints and statistical analysis section of this Synopsis.	
Rationale: This study is being conducted to characterize the PK and pharmacodynamic (PD) properties of lanadelumab and to evaluate the safety and tolerability of lanadelumab administered as a single SC dose of 300 mg in healthy subjects of Japanese descent and in matched healthy non-Hispanic, Caucasian subjects. The results of this study will be used to support the selection of the dosing regimen for a Phase 3 study conducted in Japanese patients with hereditary angioedema (HAE). The Japanese regulatory agencies, Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor and Welfare (MHLW) require evidence that current data in non-Japanese subjects can be extrapolated to the Japanese population. For this reason, the SHP643-101 study is designed to characterize PK and PD profiles, as well as to evaluate the safety and tolerability of lanadelumab in Japanese and matched non-Hispanic, Caucasian healthy volunteer subjects.	

Investigational product, dose, and mode of administration:

- Lanadelumab, 300mg SC injection into the abdomen.
- Lanadelumab is a recombinant, fully human immunoglobulin G subclass 1 (IgG1), a kappa light chain monoclonal antibody expressed in Chinese Hamster Ovary (CHO) cells. Lanadelumab is a potent (Ki = 125 pM) inhibitor of the proteolytic activity of plasma kallikrein. Lanadelumab drug product is a colorless to yellow, sterile, preservative-free solution, appearing either clear or with slight opalescence. The active ingredient, lanadelumab, is formulated using the following compendial components: 30mM sodium phosphate dibasic dihydrate, 19.6mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. Each vial contains a nominal concentration of 300 mg in 2 mL (150 mg/mL) solution. A 300 mg, single SC dose was selected for this study. For each 300 mg dose of lanadelumab, each subject will receive a total of 2 mL, which will be administered in a single 2 mL SC injection. This study is open-label and does not require the use of a placebo.

Methodology:

This study is a Phase 1, open-label, matched-control, single-dose, single-center study to evaluate the PK, safety and tolerability and PD of lanadelumab administered to healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy adult volunteer subjects. A total of 32 subjects between the ages of 18-55, inclusive will be enrolled: 16 non-Hispanic Caucasian subjects and 16 subjects of Japanese descent. Assuming a 25% dropout rate, approximately 24 subjects (12 subjects from each race/ethnicity) are expected to complete the study. Non-Hispanic Caucasian subjects will be matched to Japanese subjects based on sex (1:1 male: male, female: female), age (±5 years), and body mass index (BMI) (±15%). For example, a Japanese male, age 40 years, and BMI of 22 kg/m^2 will be matched with a Caucasian male, age 40 ± 5 years (35-45 years [inclusive]), and BMI of 22 ±15% (18.7-25.3 kg/m^2).

All subjects will receive a single dose of 300 mg of lanadelumab administered by SC injection into the abdomen.

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

Screening Period

Screening will occur within 28 days of the first dose. Subjects will be admitted to the Clinical Research Center (CRC) on Day -1.

In-House Confinement Treatment Period

- On Day 1, all subjects will receive lanadelumab as a single 300 mg SC injection into the abdomen.
- All subjects will remain in the CRC until completion of the 96 hour postdose PK sample on Day 5.

Assessments

- Serial blood samples for PK analysis will be collected for the determination of plasma lanadelumab concentrations from Day 1 predose and up to 96 hours post dose during the in-house confinement period and up to Day 112 during the out-patient visit period. These blood samples will be collected according to the Schedule of Assessments.

- Safety and tolerability including anti-drug antibodies (ADAs) will be determined through assessment of treatment-emergent adverse events (TEAEs) and vital signs, electrocardiogram (ECG) findings, and clinical laboratory evaluations on Day 1 predose and up to 96 hours postdose during the in-house confinement period and up to Day 112 during the out-patient visit period according to the Schedule of Assessments.

- Serial blood samples for PD analysis will be collected for kallikrein activity and for cleaved high molecular weight kininogen (cHMWK) from Day 1 predose and up to 96 hours postdose during the in-house confinement period and up to Day 112 during the out-patient visit period. These blood samples will be collected according to the Schedule of Assessments.

Out-Patient Visit Period

Out-patient visits will be completed on the following Study Days:

- Day 7 (± 1 day; ie, Day 6, 7, or 8)
- Day 14 (± 1 day; ie, Day 13, 14 or 15)
- Day 21 (± 1 day; ie, Day 20, 21 or 22)
- Day 28 (± 2 day; ie, Day 26, 27 28, 29, or 30)
- Day 42 (± 2 days; ie, Day 40, 41, 42, 43 or 44)
- Day 56 (± 2 days; ie, Day 54, 55, 56, 57 or 58)
- Day 84 (± 3 days; ie, Day 81, 82, 83, 84, 85, 86 or 87)
- Day 112 (± 3 days; ie, Day 109, 110, 111, 112, 113, 114 or 115)

after the single dose of investigational product is administered. Refer to Table 2 for complete details.

Inclusion Criteria:

1. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.

2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

3. Age 18-55, inclusive, at the time of consent. The date of signature of the informed consent is defined as the beginning of the Screening Period. This inclusion criterion will only be assessed at the first screening visit.

4. Subjects must be either:

   a. A subject of Japanese descent born in Japan, who has resided outside of Japan for no longer than 5 years and is of Japanese parentage, defined as having 2 Japanese parents and 4 Japanese grandparents, all born in Japan

   b. A non-Hispanic, Caucasian subject who has 2 non-Hispanic, Caucasian parents and 4 non-Hispanic, Caucasian grandparents

5. Male or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of nonchildbearing potential.

6. Considered “healthy” by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, as well as a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.

7. Body mass index between 18.5-33 kg/m², inclusive, with a body weight ≥45 kg (99lbs). This inclusion criterion will only be assessed at the screening visit.

8. Willing and able to consume standardized meals during the confinement period of the study. All participants will be required to consume the identical meals on study days when serial PK and PD blood samples are collected.

Exclusion Criteria:

1. History 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 clinical or laboratory assessments.

2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to complete the study, or any condition that presents undue risk from the investigational product or procedures.

3. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.

4. Significant illness, as judged by the investigator, within 2 weeks of the dose of investigational product.

5. Known history of alcohol or other substance abuse within the last year, per the investigator.

6. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the dose of investigational product.

7. Within 30 days prior to the dose of investigational product:

   a. Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).

   b. Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.

8. Confirmed systolic blood pressure (BP) >139mmHg or <89mmHg, and diastolic BP >89mmHg or <49mmHg.

9. Twelve-lead ECG values (average of triplicate readings) demonstrating QTc >450msec (males) or >470msec (females) at the Screening Visit or Day -1.

10. Positive screen for drugs of abuse (i.e. amphetamines, benzodiazepines, barbiturates, cocaine, marijuana, opiates, phencyclidine) at Screening, or drugs of abuse or alcohol on Day -1.

11. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. One alcohol unit=1 beer or 1 wine (5oz/150mL) or 1 liquor (1.5oz/40mL) or 0.75oz alcohol.

12. Positive HIV, HBsAg, or HCV antibody screen.

13. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the dose of investigational product.

14. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. One caffeine unit is contained in the following items: one 6oz (180mL) cup of coffee, two 12oz (360mL) cans of cola, one 12 oz cup of tea, and three 1oz (85g) chocolate bars. Decaffeinated coffee, tea, or cola are not considered to contain caffeine).

15. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of stable hormonal replacement therapy or hormonal contraceptives). Current use is defined as use within 14 days of the dose of investigational product. See Section 5 (Prior and Concomitant Treatment) for a list of permitted medications.

16. Abnormal laboratory values considered clinically significant, as determined by the investigator at Screening or Day -1.

17. History of any clinically significant surgery or procedure within 8 weeks of receiving the dose of investigational product, as determined by the investigator.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: 28 days maximum
- Planned duration of in-house confinement period: 5 days
- Planned duration of out-patient visit period: 107 days

Endpoints and statistical analysis:

Pharmacokinetic endpoint(s)/parameters:

- C_{max}: Maximum observed plasma drug concentration
- t_{max}: Time to reach C_{max} in plasma
- $AUC_{0\text{-}last}$: 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
- λ_z: Terminal elimination rate constant
- $t_{½}$: Terminal half-life
- CL/F: Apparent clearance
- $Vd_{z/F}$: Apparent volume of distribution

Safety is the secondary objective of this study. Safety endpoint(s):

- Treatment-emergent adverse events: Number and percentage of subjects with TEAEs; severity; seriousness; causality; number of TEAEs.
- Clinical laboratory results (hematology, clinical chemistry, coagulation and urinalysis): Changes from baseline to post-baseline time points; clinically significant abnormal laboratory assessments.
- Other: Vital signs (including BP, pulse, body temperature), 12-lead ECG, and physical examination: Changes from baseline to post-baseline time points.
- Anti-drug antibodies

Analysis populations/analysis sets:

- Safety population (Safety Analysis Set), defined as all subjects who received at least 1 dose of lanadelumab (study drug). All safety analyses will be based on the Safety population/Safety Analysis Set.
- Pharmacokinetic population (PK Analysis Set), defined as all subjects who received at least 1 dose of lanadelumab and have at least 1 evaluable postdose PK concentration value. All PK analyses will be based on the PK population/PK Analysis Set).

Statistical analysis:

No statistical hypothesis testing is planned. Analysis details will be provided in the study Statistical Analysis Plan (SAP), which will be finalized prior to study database lock. Only descriptive analysis will be performed to evaluate all primary and secondary endpoints. Summaries will be presented by racial/ethnic group (Japanese vs. non-Hispanic Caucasians), and, if appropriate, by time point. All data, including derived data, will be presented in subject data listings, and all listings will include subject's sex, age, race/ethnicity, and BMI.

- No interim analysis or Data Monitoring Committee (DMC) is planned.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments

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

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

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

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

[c] Medical history and medication history review only

[d] See Table 2 for detailed collection time points

[e] Height will be recorded at the Screening Visit only

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

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

[h] Thyroid function tests (TSH, T3, T4) will be collected as part of the biochemistry panel at Screening only.

[i] Drugs of abuse at screening, and drugs of abuse and alcohol (breath test) on Day -1 and at all out-patient visits.

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

Table 2: Detailed Schedule of Assessments

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

Table 2: Detailed Schedule of Assessments

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

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] These assessments should be performed within 60 minutes prior to dose administration.
[c] ECG's will be performed as single records at each timepoint.
[d] No PK or PD sample, or urine drug or alcohol screen should be collected for early discontinuation.

1 BACKGROUND INFORMATION

Lanadelumab (SHP643, formerly DX-2930) is a recombinant, fully human immunoglobulin G subclass 1 (IgG1), a kappa light chain monoclonal antibody expressed in Chinese Hamster Ovary (CHO) cells that has been studied in a double-blind, pivotal Phase 3 study (Study DX-2930-03), and is being studied in an on-going open-label Phase 3 study (Study DX-2930-04) to determine if it is safe and effective for the prevention of angioedema attacks in patients with hereditary angioedema (HAE).

This study is being conducted to evaluate the PK, safety and tolerability, and pharmacodynamic (PD) of lanadelumab administered as a single subcutaneous (SC) dose of 300 mg in a Japanese population in comparison with a single SC dose of 300 mg in a matched non-Hispanic, Caucasian population.

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

1.1 Indication and Current Treatment Options

Lanadelumab is in development for prevention of angioedema attacks in patients with Types I or II HAE, a rare and potentially life-threatening disease.

Lanadelumab is a recombinant, fully human IgG1, kappa light chain, monoclonal antibody expressed in CHO cells. Lanadelumab is a potent (Ki = 125 pM) inhibitor of the proteolytic activity of plasma kallikrein.

The activity, potency and, specificity of lanadelumab have been demonstrated in vitro and ex vivo and have been confirmed in clinical studies.

Hereditary angioedema is a long-term, debilitating, and potentially life-threatening disease caused by mutations in the C1-inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. HAE manifests clinically as unpredictable, intermittent attacks of SC or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia (Zuraw, 2008). Swelling may last up to 5 days; most patients suffer multiple attacks per year. HAE is an orphan disease. Its exact prevalence is unknown; however, current estimates range from 1 per 10,000 to 1 per 150,000 persons, with many authors agreeing that 1 per 50,000 is likely the closest estimate (Bygum, 2009; Goring et al., 1998; Lei et al., 2011; Nordenfelt et al., 2014; Roche et al., 2005).

Currently, HAE drugs are indicated either for prophylaxis against attacks or for treatment of acute attacks. Acute treatments include purified, plasma-derived C1-INH, recombinant C1-INH, a plasma kallikrein inhibitor, and a bradykinin type 2 (B2) receptor antagonist. While acute treatments are effective at resolving the symptoms of acute attacks, they do not prevent attacks and thus leave patients at risk of developing debilitating and potentially life-threatening attacks. Agents used for prophylaxis include purified plasma-derived C1-INH, attenuated androgens, and antifibrinolytic agents.

These currently available therapies represent an important addition to the therapeutic options for HAE patients; however, there remains a need for more optimal prophylactic therapy with improved efficacy, longer half-lives and more convenient administration frequencies.

1.2 Product Background

1.2.1 Preclinical Information

Nonclinical studies to evaluate the pharmacokinetic (PK) and toxicology of systemically administered lanadelumab have been completed in rats and cynomolgus monkeys.

Single-dose, 28-day and 6-month multidose studies of systemically administered lanadelumab in cynomolgus monkeys did not identify toxicologically significant effects at doses up to 50 mg/kg administered weekly by SC injections. Studies to evaluate male and female fertility in the cynomolgus monkey, at similar dose levels, revealed no adverse treatment-related findings. There were no adverse treatment-related findings after 28 days of IV dosing up to 50 mg/kg

In addition, results from a separate lanadelumab single-dose SC injection study to evaluate potential toxicity and toxicokinetic profiles in Sprague-Dawley rats, showed lanadelumab to be well-tolerated at up to 50 mg/kg.

Refer to the lanadelumab Investigator's Brochure for further information.

1.2.2 Clinical Information

The clinical development program for lanadelumab consists of two completed Phase 1 studies: a single-ascending dose Phase 1a Study, DX2930 01 in healthy adult subjects and a multiple-ascending dose and Phase 1b Study DX2930 02 in adult subjects with HAE; a completed pivotal, double-blind, placebo-controlled Phase 3 Study DX2930 03 (HELP Study®), and one ongoing open-label Phase 3 Study DX2930 04 (HELP Study Extension™) in adolescents and adult subjects with HAE.

Always refer to the latest version of the lanadelumab Investigator's Brochure for the overall risk/benefit assessment and the most accurate and current information regarding the metabolism, pharmacokinetics, efficacy, and safety of lanadelumab.

1.3 Risk/Benefit and Ethical Assessment

There is no anticipated benefit from taking part in this study.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This study is being conducted to characterize the PK and PD properties of lanadelumab and to evaluate the safety and tolerability of lanadelumab administered as a single SC dose of 300 mg in healthy subjects of Japanese descent and in matched healthy non-Hispanic, Caucasian subjects.

The results of this study will be used to support the selection of the dosing regimen for a Phase 3 study conducted in Japanese patients with HAE.

The Japanese regulatory agencies, Pharmaceuticals and Medical Devices Agency (PMDA), and the Ministry of Health, Labor and Welfare (MHLW), require evidence that current data in non-Japanese subjects can be extrapolated to the Japanese population. For this reason, the SHP643-101 study is designed to characterize PK and PD profiles, as well as to evaluate the safety and tolerability of lanadelumab in Japanese and matched non-Hispanic, Caucasian healthy volunteer subjects.

A number of scientific publications have suggested the similarity of the PK profiles of monoclonal antibody products between ethnic healthy subjects groups (Chiba et al., 2014; Morrison et al., 2015), thereby supporting the extrapolation of safety and efficacy data from other ethnic groups to Japanese patients with HAE. This study is aimed to specifically confirm this observation for lanadelumab administered as a single SC 300 mg dose. The study can be conducted in a clinical research facility that is located outside of Japan as long as steps are taken to ensure the Japanese subjects are verified as Japanese, as noted in Inclusion Criterion 4.

2.2 Study Objectives

2.2.1 Primary Objectives

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

2.2.2 Secondary Objectives

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

2.2.3 Exploratory Objectives

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

Endpoints corresponding to the primary and secondary objectives are defined in the Study Synopsis, and endpoints corresponding to the exploratory objective are defined in Section 9.8.2.

3 STUDY DESIGN

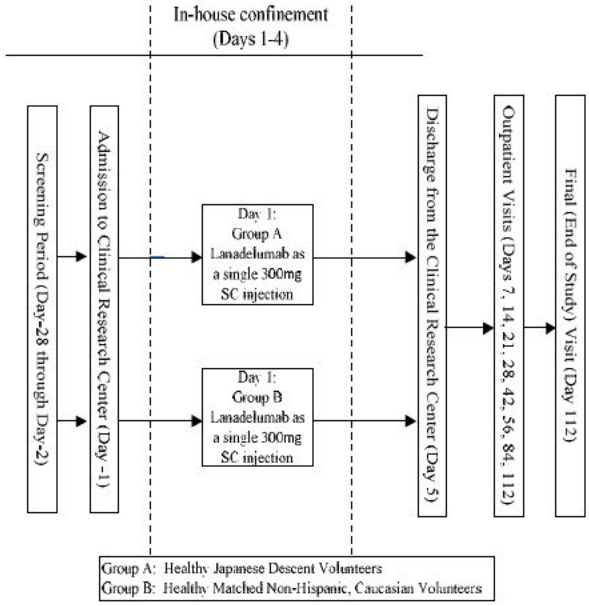
3.1 Study Design and Flow Chart

This is a Phase 1, open-label, matched-control, single dose, single-center study to evaluate the PK, safety and tolerability and PD of lanadelumab administered to healthy adult volunteer subjects of Japanese descent and matched non-Hispanic Caucasian healthy adult volunteer subjects. A total of 32 subjects between the ages of 18-55, inclusive, will be enrolled: 16 non-Hispanic, Caucasian subjects and 16 subjects of Japanese descent. Assuming a 25% dropout rate, approximately 24 subjects (12 from each race/ethnicity) are expected to complete the study. Study subjects who withdraw or discontinue early may be replaced at the discretion of the sponsor. Non-Hispanic Caucasian subjects will be matched in a 1:1 ratio to Japanese subjects based on sex (1:1 male: male, female: female), age (±5 years), and body mass index (±15%). For example, a Japanese male, age 40 years, and body mass index (BMI) of 22 kg/m^2 will be matched with a Caucasian male, age 40 ±5 years (35-45 years [inclusive]), and BMI of 22 ±15% (18.7-25.3 kg/m^2). Matching is intended to ensure that the ethnic/racial groups are comparable at baseline with respect to the matching factors. All subject volunteers will receive a single SC dose 300mg of lanadelumab in the abdomen on Day 1.

In lanadelumab clinical studies to date, there have been no dose limiting toxicities, and dose-exposure responses have been linear. No ethnic differences in the PK of lanadelumab between Japanese and non-Japanese subjects are expected, similarly to the findings reported for other monoclonal antibody drug products (Rosario et al., 2017); therefore, 300 mg, the highest dose used in Phase 3 clinical trials, will be tested in this study.

Figure 1: Study Design Flow Chart

The study design is shown in the following schematic figure:



3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 140 days. The study is expected to be completed in approximately 20 weeks.

The Study Completion Date is defined as the date the final subject completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This study will be performed at one study site within the United States.

4 STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

Subjects cannot be enrolled before all inclusion criteria (including test results) are confirmed.

1. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Age 18-55, inclusive, at the time of consent. The date of signature of the informed consent is defined as the beginning of the Screening Period. This inclusion criterion will only be assessed at the first screening visit.
4. Subjects must be either:

    a. A subject of Japanese descent born in Japan, who has resided outside of Japan for no longer than 5 years and is of Japanese parentage, defined as having 2 Japanese parents and 4 Japanese grandparents, all born in Japan.

    b. A non-Hispanic, Caucasian subject who has 2 non-Hispanic, Caucasian parents and 4 non-Hispanic, Caucasian grandparents.
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. Considered "healthy" by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, as well as a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
7. Body mass index between 18.5-33 kg/m², inclusive, with a body weight ≥45 kg (99lbs). This inclusion criterion will only be assessed at the screening visit.
8. Willing and able to consume standardized meals during the confinement period of the study. All participants will be required to consume the identical meals on study days when serial PK and PD blood samples are collected.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. History 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 clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
4. Significant illness, as judged by the investigator, within 2 weeks of the dose of investigational product.
5. Known history of alcohol or other substance abuse within the last year, per the investigator.
6. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the dose of investigational product.
7. Within 30 days prior to the dose of investigational product:
    a. Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    b. Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study.
8. Confirmed systolic blood pressure (BP) >139mmHg or <89mmHg, and diastolic BP >89mmHg or <49mmHg.
9. Twelve-lead ECG values (average of triplicate readings) demonstrating QTc >450msec (males) or >470msec (females) at the Screening Visit or Day -1.
10. Positive screen for drugs of abuse (ie, amphetamines, benzodiazepines, barbiturates, cocaine, marijuana, opiates, phencyclidine) at Screening, or drugs of abuse or alcohol on Day -1.

11. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. One alcohol unit=1 beer or 1 wine (5oz/150mL) or 1 liquor (1.5oz/40mL) or 0.75oz alcohol.
12. Positive HIV, HBsAg, or HCV antibody screen.
13. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the dose of investigational product.
14. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. One caffeine unit is contained in the following items: one 6oz (180mL) cup of coffee, two 12oz (360mL) cans of cola, one 12oz cup of tea, and three 1oz (85g) chocolate bars. Decaffeinated coffee, tea, or cola are not considered to contain caffeine.
15. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of hormonal replacement therapy or hormonal contraceptives). Current use is defined as use within 14 days of the dose of investigational product. See Section 5 (Prior and Concomitant Treatment) for a list of permitted medications.
16. Abnormal laboratory values considered clinically significant, as determined by the investigator at Screening or Day -1.
17. History of any clinically significant surgery or procedure within 8 weeks of receiving the dose of investigational product, as determined by the investigator.

4.3 Restrictions

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the clinical research center (CRC) and during the in-house stays at the CRC.
2. Subjects should refrain from alcohol 48 hours prior to admission to the CRC and during the in-house stay at the CRC (Day 1-5) and 48 hours prior to each outpatient visit during the study.
3. Subjects must refrain from use of tobacco or any products containing nicotine within 30 days of Day 1 of the treatment period through the completion of the last treatment period.
4. Subjects should refrain from taking or regularly using any medication (including over-the counter multivitamin, herbal, or homeopathic preparations) with the exception of those listed in Section 5.2.1 from 14 days prior to receiving the dose of the investigational product through the completion of the discharge assessments and procedures.
5. Subjects should refrain from foods or beverages containing caffeine/xanthine 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
6. Subjects will be required to follow standardized meal schedules and eat the meals provided by the site while housed in the CRC. No outside food or beverages (including gum, mints, etc.) will be permitted. Menus will be identical for all subjects at the CRC. Copies of the menus will be provided to the sponsor for approval prior to the start of the study.

While confined, the total daily nutritional composition should be approximately 50% carbohydrate, 35% fat, and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.4 Reproductive Potential

4.4.1 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 and for 112 days following the 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 and 112 days following the dose of investigational product.

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 acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and, at least, 6 weeks post-sterilization, or
- Females of childbearing potential with a negative urine and/or 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.

4.4.2 Male Contraception

Male subjects must be advised to use acceptable contraceptives throughout the study period and for 160 days following the dose of investigational product. Male subjects must be advised not to donate sperm during the course of the study and within 160 days of the dose of investigational product. Acceptable methods of contraception for male subjects include:

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

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the early withdrawal evaluations listed in Table 2 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up (ie Day 112/ End of Study Visit). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and date of stopping investigational product must be recorded in the case report form (CRF) and source documents.

Subjects who withdraw or discontinue early may be replaced (if needed) at the discretion of the sponsor, to ensure that approximately 24 subjects (12 from each race/ethnicity) complete the study.

4.5.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event (AE)
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Other Bygum, 2009

4.5.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, and nonpharmacological treatments such as psychotherapy as appropriate) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date of the dose of investigational product. Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the date of the administration of investigational product and the end of the follow-up period (ie Day 112/ End of Study Visit), inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications listed below) during the course of the study. Any medication which is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medications (including investigational products) must be listed on the appropriate CRF page.

Medications permitted during the study are listed below:

- Hormonal contraceptives for females of childbearing potential administered according to the package insert (see Section 4.4.1)
- Stable hormone replacement therapy ≥3 months prior to dose of investigational product
- Occasional use of a nonsteroidal anti-inflammatory drug as prescribed by the principal investigator or delegate.

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is lanadelumab (SHP643, formerly known as DX-2930), which will be provided in 300mg vials for SC injection. Additional information is provided in the current lanadelumab Investigator's Brochure.

6.1.1 Blinding the Treatment Assignment

Not Applicable.

6.2 Administration of Investigational Product

6.2.1 Allocation of Subjects to Treatment

This is an open-label single-center study.

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

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

6.2.2 Dosing

After the subject completes the screening process and is found to be eligible for dosing, the subject will receive a single 300mg lanadelumab SC injection in the abdomen on Day 1 of the in-house confinement period.

A full description of the details and preparation and administration of investigational product will be provided in a Pharmacy and Investigational Product Administration Manual, provided separately.

6.2.3 Unblinding the Treatment Assignment

Not Applicable.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product container.

All investigational product is labeled with a minimum of the protocol number, dosage form (including product name), directions for use, storage conditions, expiry date (if applicable), Lot number and/or packaging reference, the statements “For clinical trial use only” and/or “CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use,” and “Keep out of reach of children,” and the sponsor's name and address.

Space is allocated on the label so that the site representative can record a unique subject identified and initials.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier and initials on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented on the CRFs and/or other investigational product record.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated contract research organization [CRO]). For unused supplies where the originally supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, interactive response technology [IRT]) do not require a shipment form. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. The investigator/nominated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time, date, dose level) will be captured in the appropriate CRF.

6.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not applicable.

7 STUDY PROCEDURES

7.1 Study Schedule

See Table 1 and Table 2 for study procedures. The following "priority order" will be in effect when more than 1 procedure or assessment is required at a particular time point.

- Spontaneous or solicited AE reporting
- Electrocardiogram (ECG)
- Vital signs
- Clinical laboratory tests
- Pharmacokinetic blood sampling
- Anti-drug antibody (ADA) sampling
- Pharmacodynamic blood sampling
- Physical examination

NOTE: Blood sampling for PK and PD evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate CRF.

7.1.1 Screening Period

Screening procedures must be completed within 28 days prior to receiving the dose of investigational product. All screening assessments and procedures are to be performed by the principal investigator or a qualified designee. See Table 1 for a complete list of screening procedures to be performed.

Written, signed, and dated informed consent from the subject prior to the performance of any study-related procedures must be obtained by the principal investigator or a designee. A copy of the signed informed consent form must be given to the subject for their records.

7.1.1.1 Screening Failure

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been enrolled or administered investigational product.

7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing may be rescreened based on investigator discretion and sponsor approval should their availability to participate fall outside the screening window. In these cases, a new screening number must be assigned for each subject who is rescreened and a new informed consent form must be signed.

7.1.2 Treatment Period

7.1.2.1 In-house Confinement Period (Day 1 to Day 5)

Study assessments for Day 1 to Day 5 of the in-house confinement treatment period are outlined in Table 1 and Table 2. Administration of investigational product will occur on Day 1 (for all study subjects) of the in-house confinement treatment period.

Subjects will be discharged from the CRC following completion of the last study assessment on Day 5 of the in-house confinement period.

7.1.2.2 Out-Patient Visit Period (Day 6 to Day 112)

The out-patient visit period for this protocol begins following discharge on Day 5, and continues until the last out-patient visit (Day 112 ± 3 days). During this out-patient period, subjects will return to the CRC for 8 visits in order to complete scheduled assessments and procedures (as detailed in Table 1 and Table 2).

These assessments include: blood and urine samples for clinical safety labs including pregnancy for all females, blood samples for PK and PD assessments, urine for drug and alcohol testing, physical examination (including weight), vital signs (including BP, pulse, and oral body temperature), ECG, serious adverse events (SAEs), AEs, and concomitant medications.

7.1.2.3 Final Visit (Day 112)

The final visit will be the Day 112 (±3 days) out-patient visit. This visit also serves as the follow-up visit for this study. Refer to Table 1 and Table 2 for outlined study assessments and procedures. All AEs and SAEs that are not resolved by the last study visit (Day 112) will be followed to closure (see Section 8.1).

7.1.3 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Demographic information will be collected at the initial screening visit. Information to be collected will include:

- Date of birth
- Sex
- Race and ethnicity

7.2.2 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the precise protocol-scheduled time. Any safety assessment that deviates from the scheduled assessment time set forth in the protocol by more than ±15 minutes will be considered a protocol deviation.

Adverse events, prior medication, and concomitant medication use will be assessed and monitored from the time the subject signs the informed consent form to completion of the study (including to time of screen failure or drop out/discontinuation). During the study, subject safety will be closely monitored by vital sign measurements, ECG measurements, clinical safety labs, and physician oversight.

7.2.2.1 Medical and Medication History

A complete medical and medication history will be collected at the screening visit and time points described in Table 1 and Table 2 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded in the source records (and entered in the CRF), which will include:

- Recent use of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

7.2.2.2 Physical Examination (Including Height and Weight)

A complete physical examination will be performed at the time points described in Table 1 and Table 2 by a qualified licensed physician, physician's assistant, or nurse practitioner.

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)

Clinically significant abnormalities identified at the screening visit will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit will be captured as AEs on the AE CRF page, as deemed by the investigator.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.2.4 Vital Signs

Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Table 1 and Table 2 of this protocol. Additional BP and pulse rate measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE.

The same method for obtaining BP measurement (auscultatory or oscillometric) should be used throughout the study for all subjects (and documented). In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, in order to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The bladder deflation rate should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/s (and the first and last audible sounds recorded as systolic and diastolic pressure) after at least 5 minutes of rest in the assumed position.

The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

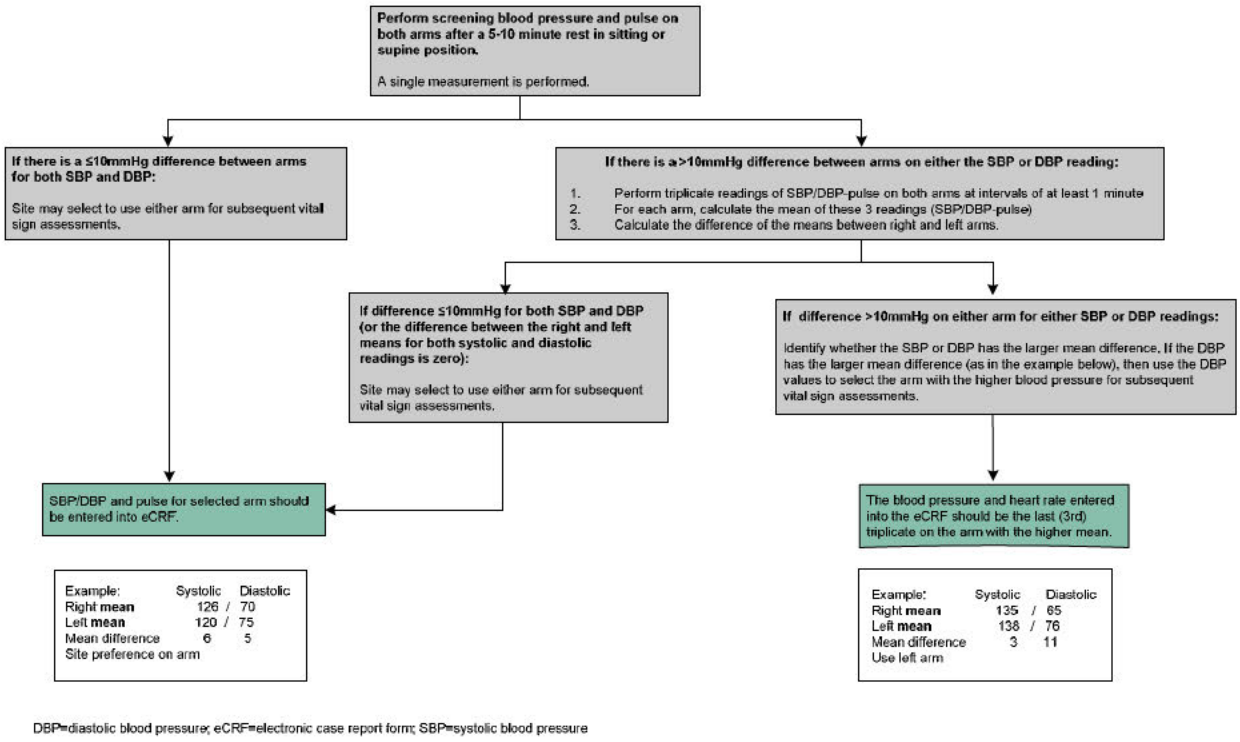
The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within the time frame(s) outlined in the Restrictions Section 4.3. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The subject should be lying comfortably, with the legs uncrossed. The arm should be supported with a pillow, such that the middle of the cuff on the upper arm is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

At the screening visit, BP should be compared between both arms. When there is a consistent inter-arm difference confirmed over 3 consecutive measurements (>10 mmHg), the arm with the higher BP should be used for inclusion at screening and the last measurement recorded in the CRF. The same (right or left) arm with the higher BP will be used throughout the study.

For details on BP and pulse procedures for healthy subjects, see Figure 2.

Figure 2: Procedures for Screening Vital Signs (Blood Pressure – Pulse) – Healthy Subjects Only



DBP=diastolic blood pressure; eCRF=electronic case report form; SBP=systolic blood pressure

One reading (supine systolic BP/diastolic BP, and pulse) should be taken.

The use of automated devices for measuring pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP, and pulse rate should be obtained prior to the nominal time of the blood collection.

Body Temperature

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Please refer to Table 1 and Table 2 for the timepoints when oral temperature will be collected.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

Blood samples (8.5 mL) for serum biochemistry will be collected into a red top gel separator tube at the time points described in Table 1 and Table 2. The following parameters will be assessed:

Sodium	Phosphorus	β-hCG [b]
Potassium	Total protein	FSH [b]
Glucose	Total CO_2 (Bicarbonate)	
Blood urea nitrogen	Albumin	
Creatinine	Aspartate transaminase	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH) [a]	Alkaline phosphatase	
Thyroxine (T4 total) [a]	Total bilirubin	
Triiodothyronine (T3) [a]	Uric acid	

[a] Collected at Screening only.
[b] Females only (Please refer to Table 1 and Table 2 for collection timepoints).

Hematology

Blood samples (4mL) for hematology will be collected into a K_2-EDTA tube at the time points described in Table 1 and Table 2.

The following parameters will be assessed:

Hemoglobin	Total neutrophils (absolute)
Hematocrit	Eosinophils (absolute)
Red blood cells	Monocytes (absolute)
Platelet count	Basophils (absolute)
White blood cell count; total and differential	Lymphocytes (absolute)

Coagulation

Blood samples (2.7mL) for coagulation will be collected into a sodium citrate tube at the time points outlined in Table 1 and Table 2. The following parameters will be assessed:

PT	PTT	INR

Urinalysis

A urine sample for urinalysis will be collected at the time points described in Table 1 and Table 2. The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.2.6 Pregnancy Test

A serum β-HCG pregnancy test is to be performed on all females at the timepoints outlined in Table 1 and Table 2; if pregnancy is suspected; or on withdrawal of the subject from the study.

7.2.2.7 Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol (breath test) will be performed at the time points described in Table 1 and Table 2. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiate metabolite, and phencyclidine.

Results of urine drug and alcohol (breath test) screens will be reviewed and verified by the study monitor, but will not be collected in the 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 timepoint after the subject has been dosed, the principal investigator must contact the Sponsor's Medical Monitor to discuss and review the circumstances, and determine whether the subject may continue in the study. Details of the discussion and decision taken must be properly recorded in the subject's source documents.

7.2.2.8 Serology Screen

At the screening visit, a blood sample of approximately 8.5mL will be drawn into a serum separator tube to test for the presence of HIV, HBsAg, and HCV antibody.

The test results must be confirmed negative prior to enrollment in the study. If a test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

7.2.2.9 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1 and Table 2. Triplicate ECGs will be performed at Screening and Day -1 only. Thereafter, single ECG recordings will be performed at all subsequent timepoints. All ECGs will be performed using the equipment supplied by the CRC.

The following parameters will be recorded on the appropriate CRF page: heart rate, PR, RR, QRS, and QT intervals. The QTcB and QTcF will be derived from the data in the database. The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing and recorded in the CRF.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within the timeframe as described in the Restrictions Section 4.3. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

Triplicate ECG Recordings – (Screening and Day -1)

Triplicate recording, including a 10-second rhythm strip, will be obtained approximately 2-4 minutes apart at the initial Screening Visit and at check in to the CRC on Day -1. Each ECG parameter obtained with the 3 assessments will be recorded in the CRF. The average of the triplicate ECG measurements collected at each nominal time point will be used for analysis. The 3 recordings should be immediately assessed as valid recordings and if not valid, they should be repeated in order to obtain a total of 3 valid recordings. Invalid recordings will not be entered in the CRF.

Single ECG Recordings – (Day 1 through Day 112)

One complete recording, including a 10-second rhythm strip, should be taken at all time points except at the initial Screening Visit and at check in to the CRC on Day -1. It should be immediately assessed as a valid recoding and if not valid, it should be repeated. Invalid recordings will not be entered in the CRF.

When a single ECG recording is performed at each time point, the ECG collected predose on Day 1 will serve as the subject's baseline ECG.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the QTcF interval (calculated online on site) is increased by >45msec from the baseline or an absolute QTcF value is >500msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>4 msec from the baseline; or is >500msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTcF values remain above 500msec (or >45msec from the baseline) for >4 hours (or sooner at the discretion of the investigator) or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to <500msec (or to <45msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

If a machine-read QTcF/QTcB value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF/QTcB values are in the acceptable range.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory for this study will be maintained in the investigator's files at the study site and in the Trial Master File at the sponsor.

Actual pharmacokinetic blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all pharmacokinetic blood samples at the precise protocol scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours postdose or by more than ±15 minutes for samples drawn beyond 4 hours postdose. Samples drawn outside these parameters will be considered a protocol deviation.

7.2.3.1 Pharmacokinetic Sample Collection and Handling Procedures

Pharmacokinetic blood samples will be collected at the time specified in Table 1 and Table 2 to measure plasma concentrations of lanadelumab. A full description of the PK blood collection, handling, storage, and shipping can be found in the provided laboratory manual.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CRC. The labels will contain the following information:

- Study number
- Subject identifier
- Nominal day
- Nominal time
- Matrix identifier (plasma)
- Split (primary or backup)

7.2.3.2 Shipment of Plasma Pharmacokinetic Samples

Instructions for shipment of all PK samples (along with the corresponding documentation) can be found in the laboratory manual provided under a separate cover.

Pharmacokinetic samples will be stored nominally at -70(±10)°C prior to and after analysis at the CRO until further directions are authorized by Shire.

7.2.3.3 Plasma Drug Assay Methodology

Plasma sample analysis will be performed according to Shire Standard Operating Procedure BC-104 (current version). Under circumstances where this Shire Standard Operating Procedure does not apply, relevant TGA Sciences (the bioanalytical lab) Operating Procedures will be followed.

Plasma concentrations will be measured using the most current validated bioanalytical method. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.2.4 Pharmacodynamic Assessments

The names and addresses of the bioanalytical laboratories for this study will be maintained in the investigator's files at the site and in the Trial Master File at the sponsor.

Actual PD blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PD blood samples at the precise protocol scheduled time. Pharmacodynamic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours postdose or by more than ±15 minutes for samples drawn at 4 hours post dose and beyond while in the CRC. For PD samples drawn during the out-patient visits refer to Table 2 for time point parameters. Samples drawn outside the parameters set forth in the protocol will be considered a protocol deviation.

7.2.4.1 Pharmacodynamic Sample Collection and Handling Procedures

Pharmacodynamic blood samples will be collected at the time specified in Table 1 and Table 2 to measure plasma concentrations of kallikrein activity and cHMWK. A full description of the PD blood collection, handling, storage and shipping can be found in the provided laboratory manual. Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CRC. The labels will contain the following information:

- Study number
- Subject identifier
- Nominal day
- Nominal time
- Matrix identifier (plasma)
- Analyte (kallikrein activity or cHMWK)
- Split (primary or backup)

7.2.4.2 Shipment of Plasma Pharmacodynamic Samples

Instructions for shipment of all PD samples (along with the corresponding documentation) can be found in the laboratory manual provided under a separate cover.

Pharmacodynamic samples will be stored nominally at -70(±10)°C prior to and after analysis at the CRO until further direction is authorized by Shire.

7.2.4.3 Plasma Pharmacodynamic Assay Methodology

Plasma levels of kallikrein activity and cHMWK will be measured using the most current validated bioanalytical methods. The presence of other metabolites or artifacts may be monitored or quantified as appropriate. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.2.5 Immunogenicity Testing for Anti-Drug Antibodies

The name and address of the bioanalytical laboratory conducting ADA immunogenicity testing for this study will be maintained in the investigator's files at the study site and in the Trial Master File at the sponsor.

Actual ADA blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all anti-drug blood samples as the precise protocol scheduled time. Anti-drug antibody blood collection will be collected on Day 1 prior to dose (within 60 minutes of dose). See Table 2 for a detailed schedule of time points. A full description of the ADA blood collection, handling, storage and shipping can be found in the provided laboratory manual.

In the event anti-drug antibodies are detected following analysis for a subject, the investigator will be notified by the sponsor. It will be the investigator's responsibility to notify the subject.

7.2.6 Volume of Blood to Be Drawn from Each Subject

Table 3: Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples [a]		5	14	70
Pharmacodynamic (cHMWK and plasma kallikrein activity) samples		5	14	70
HBsAg, HIV, HCV		8.5	1	8.5
Safety	Biochemistry, FSH and β-hCG [a,b,c]	8.5	12	102
	Hematology	4	12	48
	Coagulation (PT, aPTT, INR)	2.7	11	29.7
Anti-Drug Antibody samples		3	5	15
Total mL				**343.2**

β-hCG=beta-human chorionic gonadotropin; FSH = follicle stimulating hormone; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; TSH=thyroid stimulating hormone; T3=triiodothyronine; T4= thyroxine

[a] If a catheter is used for any blood draw or series of blood draws then the first 1mL is to be discarded. The 1mL discard has been taken into account in the table above and the total blood volume required for this study.

[b] β-hCG and FSH testing for females only.

[c] TSH, T3 and T4 will be included in the biochemistry panel, and collected at Screening only.

During this study, it is expected that approximately 343.2mL 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 343.2mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.2.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE 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: A type of AE that is usually alleviated with 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 subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.2.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire 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 post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** –Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose

- **Medication Error** –An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

The administration of investigational product to an eligible volunteer following a temperature excursion as outlined in the pharmacy manual, without assessment of the excursion and permission of the sponsor to proceed is deemed a medication error.

It is not expected that overdose would occur in this study. The investigational product used in this study is supplied in 1strength (300 mg) and is administered once per volunteer by a trained and responsible staff member at the study site with sponsor oversight.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the lanadelumab Investigator's Brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.6) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Drug Safety Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" 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 which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.2.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities/US Central Institutional Review Board (IRB) of related, unexpected SAEs.

In addition the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP643 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are to be documented in an auditable manner.

9.3 Data Handling Considerations

All analyses/summaries will be based on observed data, with no imputation for missing data, unless otherwise specified in the study Statistical Analysis Plan (SAP).

9.4 Statistical Analysis Process

No statistical hypothesis testing is planned. Analysis details will be provided in the SAP.

Study data will be analyzed by the sponsor or its agent (CRO)**.** To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to study database lock. The SAP will provide the statistical methods and definitions for the analysis of the pharmacokinetic, pharmacodynamic, and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

Descriptive analysis will be performed to evaluate all primary, secondary and exploratory endpoints, and the following, including the definition below, will apply:

- Continuous endpoints (eg, change in parameter) will be summarized, displaying: number of subjects (n), mean, standard deviation (SD), median, minimum and maximum value. As appropriate, raw (actual) values, changes from baseline, and percent changes from baseline will be summarized overall and at each scheduled timepoint. Baseline is defined as the last non-missing value prior to dosing with investigational product (lanadelumab). Additional summary statistics will be provided for pharmacokinetic and pharmacodynamics endpoints and are indicated in Sections 9.8.1 and 9.8.2.
- Categorical endpoints (eg, presence or absence of an outcome measure) will be summarized, displaying counts and percentages. Summaries will include, where applicable: number and percentage of subjects with an outcome measure and shift tables (categorical change from baseline).Summaries will be presented by racial/ethnic group (Japanese vs. non-Hispanic Caucasians), and, if appropriate, by timepoint. Matching of non-Hispanic Caucasian subjects to Japanese subjects, according to the study design, is intended to ensure that the ethnic/racial groups are comparable at baseline with respect to the matching factors (sex, age, and body mass index). All subject volunteers will receive a single SC dose 300mg of lanadelumab in the abdomen on
  Day 1.

All data, including derived data, will be presented in subject data listings and all listings will include subject's sex, age, race/ethnicity, and body mass index.

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

No interim analysis, adaptive design, or Data Monitoring Committee (DMC) is planned.

9.6 Sample Size Calculation and Power Considerations

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

Assuming a 25% dropout rate, the sample size ensures approximately 24 subjects (12 Japanese and 12 matched Caucasians) complete the study, and 24 subjects are evaluable for pharmacokinetic analysis purposes. The sample size is considered adequate for the primary and secondary objectives of the study and therefore adequate for providing reliable estimates of pharmacokinetic parameters.

The sample size was based on clinical judgment and precedent pharmacokinetic studies of similar design and similar subject population and not on statistical considerations such as study power. Subjects who prematurely discontinued the study, whether subjects are part of matched pairs or are not yet matched, may be replaced at the discretion of the study sponsor to ensure there are approximately 12 evaluable subjects in each racial/ethnic group for pharmacokinetic analysis purposes.

9.7 Analysis Populations/ Analysis Sets

Safety, PK and PD analyses will be based on the following subject populations (analysis sets), as defined:

- Safety population (Safety Analysis Set): All subjects who received at least 1 dose of lanadelumab (study drug).
- Pharmacokinetic population (PK Set): All subjects who received at least 1 dose of lanadelumab and have at least 1 evaluable postdose PK concentration value.
- Pharmacodynamic population (PD Analysis Set): All subjects who received at least 1 dose of lanadelumab and have at least 1 evaluable postdose PD concentration value.
- Enrolled Set: All subjects for whom an enrollment number has been assigned.

9.8 Pharmacokinetic and Pharmacodynamic Analyses

9.8.1 Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated using plasma concentration-time data by non-compartmental methods and all calculations will be based on actual sampling times.

Baseline is defined as the Day 1 predose concentration. Pharmacokinetic parameters will be estimated by noncompartmental analysis and will include, but not be limited to, the following:

- C_{max}: Maximum observed plasma drug concentration
- t_{max}: Time to reach C_{max} in plasma
- $AUC_{0\text{-}last}$: 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
- λ_z: Terminal elimination rate constant
- $t_{½}$: Terminal half-life
- CL/F: Apparent clearance
- $Vd_{z/F}$: Apparent volume of distribution

Body weight-adjusted AUClast, Cmax, CL/F, and Vdz/F will be estimated as well.

9.8.1.1 Statistical Analysis of Pharmacokinetic Parameters

Pharmacokinetic parameters of lanadelumab and plasma concentrations at each nominal sampling time will be provided in subject data listing(s) and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean), presented by racial/ethnic group (Japanese vs non-Hispanic, Caucasian). In addition, 95% confidence intervals for key PK parameters will be provided as appropriate, as well as graphs of individual and mean (± SD) concentration-time profiles plasma lanadelumab and graph(s) of observed and weight-adjusted PK parameters (y-axis) versus body weight (x-axis).

All plasma concentration values below the lower limit of quantification (LLOQ) will be set to zero when calculating summary statistics. For the calculation of PK parameters, all plasma concentrations that are LLOQ prior to the first measurable concentration will be set to zero. The LLOQ values that are between measurable concentrations will be set to missing. The LLOQ values following the last quantifiable timepoints will be set to missing. No concentration estimates will be imputed for missing sample values. Any sample with a missing value will be treated as if the sample had not been scheduled for collection and will be ignored when calculating mean concentrations or PK parameters.

Pharmacokinetic analysis will be based on the Pharmacokinetic population.

9.8.2 Pharmacodynamic Analysis

Pharmacodynamic assessment is an exploratory objective of the study. Individual subject plasma kallikrein activity and plasma cHMWK with and without baseline correction will be provided in subject data listings and summarized using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and %CV of geometric mean), presented by racial/ethnic group (Japanese vs. non-Hispanic, Caucasian).

In addition, 95% confidence intervals will be provided as appropriate. Graphs of individual and mean (±SD) activity-time profiles will be generated.

Pharmacodynamic analysis will be based on the Pharmacodynamic population.

9.8.3 Pharmacokinetic and Pharmacodynamic Analysis

Not applicable.

9.9 Safety Analyses

Safety endpoints are defined in the Synopsis section. Descriptive analysis, as described in Section 9.4 will be performed to evaluate all safety endpoints.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent adverse events (TEAEs) will be calculated overall, by system organ class, by preferred term, and by treatment group.

Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/ listed.

Only TEAEs will be analyzed. All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listing. All safety data, including derived data, will be presented in subject data listings, and all listings will include subject's sex, age, race/ethnicity, and body mass index.

Clinical laboratory tests, vital signs, and ECG findings will be summarized, as appropriate, by racial/ethnic group (Japanese vs. non-Hispanic, Caucasian) and visit. Potentially clinically important findings will also be summarized or listed in subject data listing.

Safety analysis will be based on the Safety population.

Definition

Treatment-emergent adverse events (TEAEs): TEAEs are AEs with onset at the time of or following the first exposure to study drug, or medical conditions present prior to the start of study drug but increasing in severity or relationship at the time of or following the start of treatment, up to the last follow-up visit.

9.10 Other Analyses

No other analyses are planned.

9.10.1 Exploratory Analysis

Pharmacodynamic analysis is the exploratory analysis. Refer to Section 9.8.2 for analysis.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current good clinical practice (GCP) and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or, for multicenter studies, the coordinating principal investigator, according to national provisions, and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the clinical trial agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor or investigator, or, for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market lanadelumab; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11 REFERENCES

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12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	27 Nov 2017	Global