PROTOCOL: SHP643-102

TITLE:	A Randomized, Open-label, Single-dose, Parallel-arm, Single-center, Phase 1 Study to Determine the Bioavailability of Lanadelumab Administered Subcutaneously with the Prefilled Syringe and the Autoinjector in Healthy Adult Volunteer Subjects
DRUG:	SHP643, lanadelumab (formerly DX-2930)
IND:	116647
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Dyax Corp. (a wholly-owned, indirect subsidiary of Shire plc) 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted]
PROTOCOL HISTORY:	Original Protocol: 29 Jan 2019

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

[redacted]

	Date: [redacted]
	{Note: Signature date must not precede the approval date}

Investigator's Acknowledgement

I have read this protocol for Study SHP643-102.

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

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 Council for Harmonisation guidelines of Technical Requirements for Registration of Pharmaceuticals for Human Use 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)	***{The investigator completes the bottom section of the protocol signature page}***

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by the Protocol" within 24 hours to the Shire Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO) (as applicable)/Shire Medical Monitor using the details below.

E-mail: [redacted]

For protocol- or safety-related questions or concerns <u>during normal business hours</u> the investigator must contact the Shire Medical Monitor:

[redacted]

[redacted] (Business hours)

[redacted] (24-hour coverage)

For protocol- or safety-related questions or concerns <u>outside of normal business hours</u>, the investigator must contact the Shire Medical Monitor:

[redacted]

[redacted] (24-hour coverage)

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination); or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products); or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

For instructions on reporting AEs related to product complaints, see Appendix 4.4.

Please use the information below as applicable to report the Product Quality Complaint or Non-Medical Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AI	autoinjector
aPTT	activated partial thromboplastin time
BA	bioavailability
BE	bioequivalence
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CM	concomitant medication
CRA	clinical research associate
CRC	clinical research center
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
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
HEOR	Health Economics and Outcome Research
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
PE	physical exam
PFS	prefilled syringe
PK	pharmacokinetic

PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
TEAE	treatment emergent adverse event(s)
T3	triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
US	United States
UDS	urine drug screen
VS	vital signs

STUDY SYNOPSIS

Protocol number: SHP643-102	**Drug:** lanadelumab
Title of the study: A Randomized, Open-label, Single-dose, Parallel-arm, Single-center, Phase 1 Study to Determine the Bioavailability of Lanadelumab Administered Subcutaneously with the Prefilled Syringe and the Autoinjector in Healthy Adult Volunteer Subjects	
Number of subjects (total and for each treatment arm): Approximately 176 healthy volunteer subjects will be randomized to receive lanadelumab (SHP643) administered via a prefilled syringe (PFS) or administered via an autoinjector (AI)	
Investigator(s): [redacted]	
Site(s) and Region(s): [redacted]	
Study period (planned): 2019	**Clinical phase:** 1

Objectives:

Primary: To evaluate bioavailability of lanadelumab following a single 2 mL subcutaneous (SC) dose of 300 mg delivered by prefilled syringe (PFS) or autoinjector (AI) in healthy adult subjects

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

Rationale:

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

The present bioequivalence study will compare the bioavailability of a 300 mg SC dose of lanadelumab when administered by the PFS or AI.

Investigational product, dose, and mode of administration:

- Lanadelumab, (SHP643) 300 mg PFS SC injection into the abdomen.
- Lanadelumab, (SHP643) 300 mg AI 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 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: 30 mM sodium phosphate dibasic dihydrate, 19.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, 0.01% Polysorbate 80. A 300 mg dose was selected for this study as this dose is the currently approved dose for lanadelumab. Both the PFS and the AI contain a nominal concentration of lanadelumab of 300 mg in a 2 mL (150 mg/mL) solution. For each 300 mg dose of lanadelumab, each subject will receive a total of 2 mL, which will be administered SC

in the abdomen in a single 2 mL dose using either the PFS or the AI per their randomized assignment. This study is open-label and does not require the use of a placebo.

- Comparator products in this study are the PFS versus the AI.

Methodology:

This study is a Phase 1, randomized, open-label, single-dose, parallel-arm, single-center study to evaluate the PK, safety and tolerability of 300 mg of lanadelumab administered to healthy adult volunteer subjects either via a PFS or via an AI. A total of approximately 176 subjects between the ages of 18-55, inclusive, will be enrolled.

All randomized subjects will receive a single subcutaneous (SC) 300 mg dose of lanadelumab administered into the abdomen. Fifty-percent of the subjects will receive the lanadelumab injection via a PFS, and the other 50% will receive the lanadelumab injection via an AI.

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 [± 2 days], 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. Day -1 is considered part of the screening period. Subject eligibility will be determined prior to randomization.

In-House Confinement Treatment Period

- On Day 1, all randomized subjects will receive lanadelumab as a single 2 mL 300 mg SC injection into the abdomen with either the PFS or the AI per their randomized assignment.
- All subjects will remain in the CRC until collection of the 96 hour post-dose 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 immunogenicity, will be determined through assessment of treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG), antidrug antibodies (ADAs) and clinical laboratory evaluations on 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 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 days; ie, Day 27, 28 or 29)
- 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.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent to participate in the study.
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. 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.
5. Must be considered "healthy", per the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
6. Body mass index between 18.5-33 kg/m², inclusive, with a body weight ≥45 kg (99 lbs). This inclusion criterion will only be assessed at the initial screening visit and on Day -1.
7. 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 blood samples are collected.

Exclusion Criteria:

1. Per the investigator, a 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. Per the investigator, a 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) >139 mmHg or <89 mmHg, and diastolic BP >89 mmHg or <49 mmHg.
9. Twelve-lead ECG values demonstrating QTcF >450 msec (males) or >470 msec (females) at the screening visit or Day -1. If QTcF exceeds 450 msec (males) or 470 msec (females), the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
10. Positive screen for drugs of abuse and/or disallowed drugs (ie, amphetamines, benzodiazepines, barbiturates, cocaine, opiates, phencyclidine) at screening, or drugs of abuse or alcohol on Day -1. This screen will include marijuana.

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 (5 oz/150 mL) or 1 liquor (1.5 oz/40 mL) or 0.75 oz 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 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, and three 1 oz (85 g) 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. (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 parameters:

- $AUC_{0\text{-last}}$: Area under the concentration-time curve from time zero to the last quantifiable concentration in plasma
- $AUC_{0\text{-}\infty}$: Area under the concentration-time curve from time zero extrapolated to infinity based on the predicted concentration at t_{last}
- C_{max}: Maximum observed plasma drug concentration
- t_{max}: Minimum time to reach C_{max}
- $t_{½}$: Terminal half-life
- CL/F: Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed
- Vdz/F: Apparent volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
- λ_z: First order rate constant associated with the terminal (log-linear) portion of the curve

Safety endpoints:

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

Analysis sets:

- Safety analysis set, defined as all randomized subjects who received the dose of lanadelumab

(study drug). All safety analyses will be based on the safety analysis set.

- Pharmacokinetic analysis set, defined as all randomized subjects who received the dose of lanadelumab and have at least 1 evaluable post-dose PK concentration value. All PK analyses will be based on the PK analysis set.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments

Visit	Screening		In-House Treatment Period [a]	Out-Patient Visits [b, c]	End of Study (Day 112) or Early Discontinuation
Study Day	**–28 to -02**	**-1[h]**	**1 to 5**	**7 to 112**	
Informed consent	X		Refer to Table 2	Refer to Table 3	
Inclusion/exclusion criteria	X	X			
Demography	X	X			
Medical/Medication History	X	X			X
Physical examination	X	X			X
Vital signs (blood pressure, pulse) supine	X	X			X
Body temperature (oral)	X	X			X
Height, Weight and BMI[d,e]	X	X			X
Electrocardiogram (12-lead)	X [f]	X [f]			X
Biochemistry, hematology, and urinalysis	X	X			X
TSH, T3, T4	X				
PT, aPTT, INR	X	X			X
HIV, HBsAg, and HCV antibodies	X				
Serum Pregnancy test (all females)	X	X			X
FSH (all females)	X				
Urine drug and alcohol (breath test) screening	X	X			
Pharmacokinetic blood sampling (PK)		X			
Anti-drug antibody blood sampling (ADA)		X			X
Check-in to the CRC		X			
Out-patient visits	X				X
In-patient visit		X			
Concomitant Medication	X	X			X
Adverse Event/Serious Adverse Event	X	X			X

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

[a] Refer to Table 2 for the procedures and the timing of the procedures to be done during the in-house treatment period.

[b] Refer to Table 3 for the procedures and the timing of the procedures to be done during the out-patient visits.

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

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

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

[f] Single ECG recordings are required; However, ECGs will be performed in triplicate if the QTcF interval (calculated on line on site) is increased by >45 msec from the baseline4, or an absolute QTcF value is >500 msec for any scheduled ECG, or if indicated per exclusion criteria #9 or in Section 7.2.2.9, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. Thereafter, all subsequent ECGs will be single recordings.

Table 2: Detailed Schedule of In-Patient Assessments (Days 1-5)

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

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

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

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

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

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

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

Table 3: Detailed Schedule of Out-Patient Assessments (Study Days 7-112)

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

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

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

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 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). Lanadelumab has been approved by the US Food and Drug Administration (FDA) for marketed use for the prevention of angioedema attacks in patients with hereditary angioedema (HAE).

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

1.1 Indication and Current Treatment Options

Lanadelumab has been developed for the prevention of angioedema attacks in patients with Types I or II HAE, a rare and potentially life-threatening disease, and is indicated in the US for prophylaxis to prevent attacks of HAE in patients 12 years and older (reference to the FDA label).

Lanadelumab is a potent (Ki=125 pM) inhibitor of the proteolytic activity of plasma kallikrein (pKAL).

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 subcutaneous (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 previously used for prophylaxis include purified plasma-derived C1-INH, attenuated androgens, and antifibrinolytic agents.

These currently available therapies represent important therapeutic options for HAE patients; lanadelumab has been developed as a prophylactic therapy with improved efficacy, a longer half-life and a more convenient administration frequency.

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 doses 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®), a Japanese bridging Phase 1 study (SHP643-101) in healthy adult subjects and one ongoing open-label Phase 3 Study DX2930-04 (HELP Study Extension™) in adolescent and adult subjects with HAE.

1.3 Risk/Benefit and Ethical Assessment

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

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

1.4 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 3.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

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

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

2.2 Study Objectives

2.2.1 Primary Objective

To evaluate bioavailability of lanadelumab following a single, 2 mL subcutaneous (SC) dose of 300 mg delivered by prefilled syringe (PFS) or auto injector (AI) in healthy adult subjects.

2.2.2 Secondary Objective

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

2.2.3 Exploratory Objectives

[redacted]

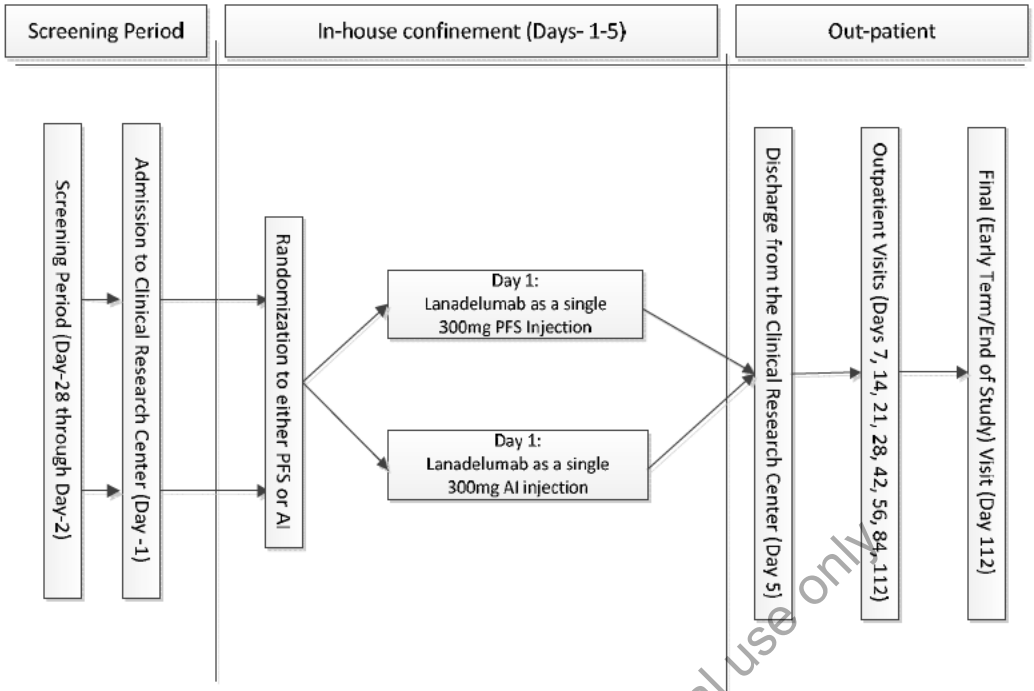
3. STUDY DESIGN

3.1 Study Design and Flow Chart

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

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

Figure 1: Study Design Flow Chart



3.2 Duration and Study Completion Definition

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

The study completion date is defined as the date on which the last subject, in the study completes the final protocol-defined assessment(s). Please note that this includes the follow-up visit or contact, whichever is later (refer to Section 7.1.3 for the defined follow-up period for this protocol).

3.3 Sites and Regions

This study will be performed at one study site in 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 randomized before all inclusion criteria (including test results) are confirmed.

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent to participate in the study.
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. 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.
5. Must be considered "healthy", per the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
6. Body mass index between 18.5-33 kg/m², inclusive, with a body weight ≥45 kg (99 lbs). This inclusion criterion will only be assessed at the screening visit and on Day -1.
7. 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 blood samples are collected.

4.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. Per the investigator, a 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. Per the investigator, a 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) >139 mmHg or <89 mmHg, and diastolic BP >89 mmHg or <49 mmHg.
9. Twelve-lead ECG values demonstrating QTcF >450 msec (males) or >470 msec (females) at the screening visit or Day -1. If QTcF exceeds 450 msec (males) or 470 msec (females), the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
10. Positive screen for drugs of abuse and/or disallowed drugs (ie, amphetamines, benzodiazepines, barbiturates, cocaine, opiates, phencyclidine) at screening, or drugs of abuse or alcohol on Day -1. This screen will include marijuana.
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 (5 oz/150 mL) or 1 liquor (1.5 oz/40 mL) or 0.75 oz 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 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, and three 1 oz (85 g) 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.

4.3 Restrictions

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRC and during the in-house stays at the CRC. In addition, subjects should refrain from strenuous physical exercise 30 minutes prior to all out-patient visits.
2. Subjects should refrain from alcohol 48 hours prior to admission to the clinical research center (CRC) and during the in-house stay at the CRC (Days 1-5) and 48 hours prior to each outpatient visit during the study.
3. Subjects should refrain from the use of tobacco or any products containing nicotine within 30 days of Day 1 of the 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) from the CRC on Day 5.
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. In addition, subject should also refrain from foods or beverages containing caffeine/xanthine 30 minutes prior to all out-patient visits.
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 menu 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, including the 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 procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and, at least, 6 weeks post-sterilization, or
- Females of childbearing potential with a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit and Day -1. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

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

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 his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

If a subject discontinues from the study, regardless of the reason, the early withdrawal evaluations listed in Table 1 are to be performed as completely as possible. Whenever possible, all discontinued subjects should complete early termination procedures. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for discontinuation and date of discontinuation must be recorded in the source documents.

Subjects who discontinue from the study will not be replaced.

4.5.1 Reasons for Study Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject discontinued for more than 1 reason, each reason should be documented in the source document.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject
- Lost to follow-up
- Other

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 received within 30 days [or PK equivalent of 5 half-lives, whichever is longer]) of the date of 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 wellbeing may be given at the discretion of the investigator. The administration of all concomitant medications must be listed on the appropriate CRF page.

Medications permitted during the study are listed below:

- Hormonal contraceptives for females of child-bearing potential administered according to the package insert (see Section 4.4.1)
- Hormone replacement therapy ≥3 months prior to dose of investigational product
- Occasional use of 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 for each subject as either a 300 mg/dose PFS or a 300 mg/dose AI for SC injection. Additional information about lanadelumab 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 screening number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting with 0001.

The actual treatment given to individual subjects is determined by a randomization schedule.

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

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

6.2.2 Dosing

After the subject completes the screening process and is found to be eligible for dosing, the subject will be randomized to receive either a single 300 mg lanadelumab SC injection in the abdomen administered via PFS or a single 300 mg lanadelumab SC injection in the abdomen administered via AI on Day 1 of the in-house confinement period. The start and stop times (to the nearest second) for IP injection (both PFS and AI) will be recorded in subject source documentation and the CRF.

A full description of the details for the preparation and administration of the investigational product and of the devices for administration will be provided in a separate Pharmacy Manual.

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, expiratory 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 identifier 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.

6.3.4 Special Handling

Refer to the SHP643-102 Pharmacy Manual for complete details regarding the lanadelumab (SHP643) investigational product and devices.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed 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 administrations of IP will be documented in the subject's source 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 CRO). For unused

supplies where the original 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, 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 will be captured in the appropriate CRF.

6.6 Retention of Bioavailability and Bioequivalence Testing Samples

In compliance with 21 CFR 320.38 (1999), and as recommended in the Center for Drug Evaluation and Research Guidance for Industry dated May 2004 regarding retention of relevant reserve (BA and BE test samples), CROs, site management organizations, or clinical investigators must retain samples when relevant BA/BE testing has been performed under contract by the sponsor. Retained samples must meet 21 CFR 320.38 (1999) and 320.63 (1999) requirements for reserve samples of test article and reference standards according to the following:

- Reserve samples must be representative of the test batches provided and therefore must be randomly selected from identical test article and/or reference standards provided to the site
- The quantity of retained samples should be sufficient optimally to permit the FDA to perform all release testing identified in the application 5 times
- Samples are adequately identified so that the reserve sample can be positively identified as having come from the same batches as used in the BA/BE studies
- Samples must be stored under conditions that maintain the identity, integrity, strength, quality, and purity of the samples.
- Samples must be retained for at least 5 years following the date of New Drug Application or supplemental New Drug Application approval or, if the Investigational New Drug is discontinued, for at least 5 years following the date of completion of the BA/BE study
- Samples must be annually inspected and documented to confirm integrity.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1, Table 2, and Table 3 for study procedures.

The following "priority order" will be in effect when more than 1 procedure or assessment are 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
- Physical examination.

NOTE: Blood sampling for PK 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 as appropriate 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 randomized 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 study 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 7-112)

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). The first out-patient visit is on Day 7. 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 3).

These assessments include: blood and urine samples for clinical safety labs including pregnancy testing for all females, blood samples for PK 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, blood samples for ADA assessments 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 3 for outlined study assessments and procedures. All AEs and SAEs that are not resolved by the last study visit (Day 112) will be followed until closure (see Appendix 4.2).

7.1.3 Additional Care of Subjects After the Study

No after care is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

- 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 in the subject's source documentation. 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 on Days 1 through 5 will be considered a protocol deviation.

Adverse events, prior medication, and concomitant medication and therapy 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 performed at the screening visit/time points described in Table 1 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

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

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, Table 2, and Table 3 by a qualified licensed physician, physician's assistant, or a 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 (per investigator) abnormalities identified at the screening visit will be documented in the subject's source documents and on the medical history CRF. Changes

(worsening in frequency or severity) 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. (Refer to Appendix 4 for AE definitions, assessment, collection time frame, and reporting procedures.)

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, Table 2, and Table 3 of this protocol. Additional blood pressure 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 blood pressure 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.

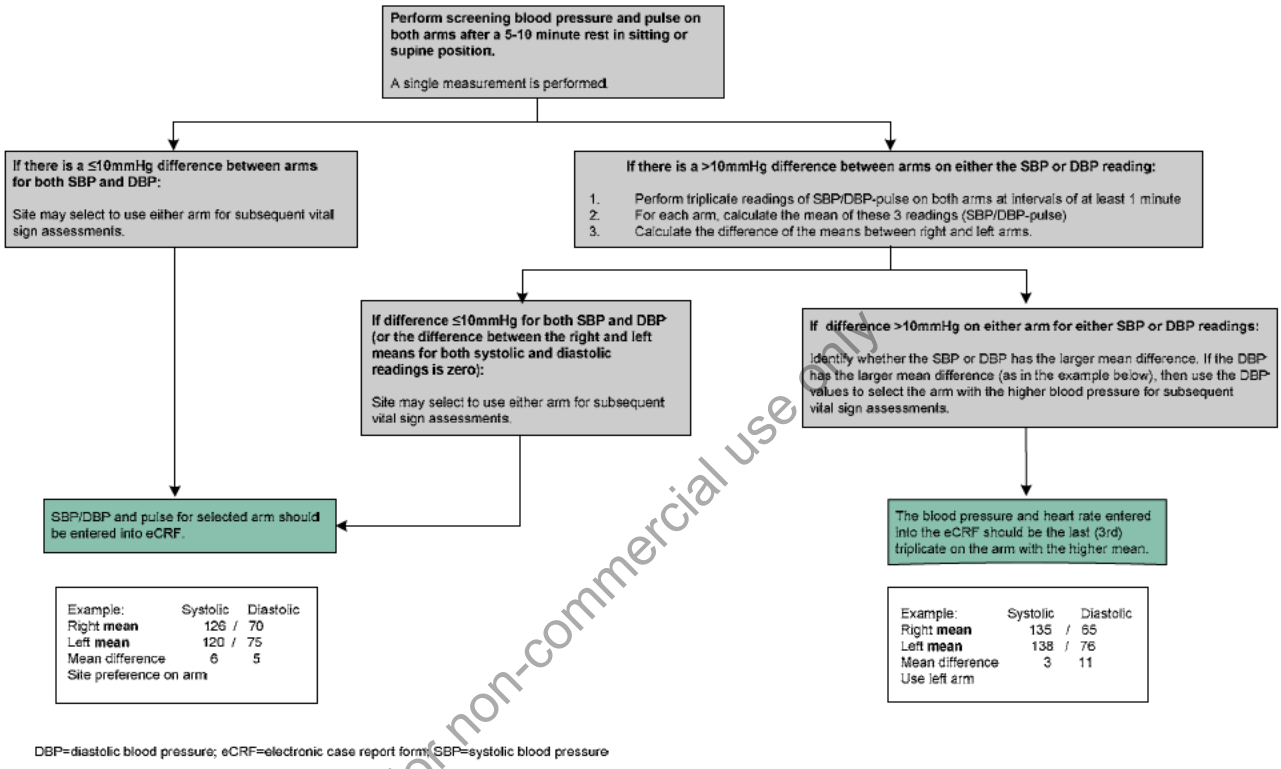
The subject should be lying comfortably, with the legs uncrossed. The arm should be supported with a pillow, such that the middle of the cuff on the upper arm is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

At the screening visit, blood pressure 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 blood pressure should be used for inclusion at screening and the last

measurement recorded in the CRF. The same (right or left) arm with the higher blood pressure will be used throughout the study.

For details on blood pressure 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 blood pressure/diastolic blood pressure-heart rate) 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, blood pressure 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.

7.2.2.5 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. 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 gel separator tube at the time points described in Table 1, Table 2, and Table 3. 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, Table 2, and Table 3 for collection time-points).

Hematology

Blood samples (4 mL) for hematology will be collected into a K_2-EDTA tube at the time points described in Table 1, Table 2, and Table 3. 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 (2.7 mL) for coagulation will be collected into a sodium citrate tube at the time points outlined in Table 1, Table 2, and Table 3. 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, Table 2, and Table 3. 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 will be performed on all females at the time points outlined in Table 1, Table 2, and Table 3 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, Table 2, and Table 3. This screen will include marijuana. Additional drug and alcohol screens may be performed at the investigator's discretion.

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

Results of urine drug and alcohol 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 time point after the subject has been dosed, the principal investigator must contact the sponsor's Medical Monitor to discuss and review the circumstances and to determine whether the subject may continue in the study. Details of the discussion taken must be properly recorded in the subject's source documents.

7.2.2.8 Serology Screen

At the screening visit, a blood sample of approximately 8.5 mL 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, Table 2, and Table 3. 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 (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 outlined 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.

One complete recording, including a 10 second rhythm strip, should be taken at each time point. It should be immediately assessed as a valid recording 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 pre-dose 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 on line on site) is increased by >45 msec from the baseline, or an absolute QTcF value is >500 msec 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 (>45 msec from the baseline; or is >500 msec), 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 500 msec (or >45 msec 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 <500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

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

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory(ies) for this study will be maintained in the investigator's files at the/each site and in the Trial Master File at the CRO.

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 post-dose or by more than ±15 minutes for samples drawn beyond 4 hours post-dose on Day 1 through Day 5 only. Samples drawn outside these parameters will be considered a protocol deviation.

7.2.3.1 Blood Sample Collection and Handling Procedures

Blood samples will be collected at the time specified in Table 2 and Table 3 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.

Pharmacokinetic samples will be stored nominally at -70°C (±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 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 assessed or quantified as appropriate. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.2.3.4 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 CRO.

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 at 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 and Table 3 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.

7.2.4 Volume of Blood to be Drawn from Each Subject

Table 4: 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
HBsAg, HIV, HCV		5	1	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				269.7

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 1 mL is to be discarded. The 1 mL 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 269.7 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 269.7 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the samples may be combined.

8. DATA MANAGEMENT AND STATISTICAL METHODS

8.1 Data Collection

The investigator's authorized site personnel must enter the information required by the protocol into CRF according to the study CRF Completion Guidelines. This study will be monitored according to ICH GCP Guidelines.

A study monitor will visit the 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. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

8.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan and according to the study CRF Completion Guidelines. 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.

8.3 Data Handling

All analyses/summaries will be based on observed data, with no imputation for missing data, unless otherwise specified in the statistical analysis plan (SAP).

8.4 Statistical Analysis Process

The study data will be analyzed by the sponsor or its agent.

Unless otherwise specified, summary tabulations will be presented by treatment group. For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. The SAP will provide the statistical methods and definitions for the analysis of the pharmacokinetic, 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.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

Pharmacokinetic analyses will be performed using Phoenix® WinNonlin® (Certara, Princeton, NJ 08540). All other statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

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

There are no planned interim analysis, adaptive design, or DMC in this study.

8.6 Sample Size Calculation and Power Considerations

The planned sample size for this study is approximately 176 subjects; 88 subjects in the PFS arm and 88 subjects in the AI arm. The sample size was calculated using SAS v9.3 based on the two one-sided tests procedure of Schuirmann on the log-transformed data.

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

8.7 Study Population

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

- The randomized set will consist of all subjects randomized to an administration type group.

- Safety analysis set: All subjects who received the dose of lanadelumab (study drug). The safety analysis set will be used for the analysis of safety endpoints

- Pharmacokinetic (PK) analysis set: All randomized subjects who received the dose of lanadelumab and have sufficient data to calculate at least 1 primary PK endpoint [$AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$ or C_{max}]. Subjects must not have protocol deviations that would impact data analysis. The PK analysis set will be used for the analysis of PK endpoints.

8.8 Analysis of Disposition

The numbers of subjects randomized, completing, or withdrawing, along with reasons for withdrawal, will be tabulated by treatment group and overall for the randomized set, safety analysis set, and pharmacokinetic analysis set.

8.9 Demographics and Baseline Characteristics Analyses

Baseline and demographic variables will be descriptively summarized by treatment group and overall for the safety analysis set, and PK analysis set.

8.10 Treatment Compliance and Extent of Exposure

It is anticipated that all patients will be compliant with treatment because the study medication will be administered in the clinic. The extent of exposure to study drug will be described by reporting the number and percentage of subjects with none or 1 injection for the safety analysis set and PK analysis set.

8.11 Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed for the subjects in the PK analysis set.

8.11.1 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 pre-dose concentration. Pharmacokinetic parameters will be estimated by non-compartmental 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 $AUC_{0\text{-}last}$, C_{max}, CL/F, and Vdz/F will be estimated as well.

8.11.1.1 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). 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 below LLOQ prior to the first measurable concentration will be set to zero. The LLOQ values below LLOQ that are between measurable concentrations will be set to missing. The values below 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.

8.12 Safety Analyses

Safety analyses will be performed for the subjects in the safety analysis set. Safety endpoints are defined in the Synopsis section. Descriptive analysis, as described in Section 8.4 will be performed to evaluate all safety endpoints.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. The number and percentage of subjects with TEAEs will be calculated overall, by system organ class (SOC), preferred term, and treatment group. Number and percentage of subjects with TEAEs will be further summarized by severity and relationship to investigational product. Subjects with TEAEs 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 listings. All safety data, including derived data, will be presented in subject data listings, and all listings will include subject's sex, age, race, weight and body mass index.

Actual values and change from baseline in clinical laboratory tests and vital signs will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.
The number and percentage of subjects with normal, abnormal-not clinically significant, and abnormal-clinically significant ECG findings will be summarized by treatment group and visit. Abnormal ECG findings will be summarized or listed.
The number and percentage of subjects with neutralizing antibody, positive, negative, or not evaluable antibody results will be summarized for each treatment group by visit and overall. Positive immunogenicity results will be summarized or listed.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Concomitant medications are medications that the subject started or continued using after the study medication administration. Number of subjects with concomitant medications will be summarized by therapeutic class, preferred term, and treatment group.

8.13 Other Analyses

[redacted]

9. REFERENCES

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10. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	01 Feb 2019	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	**Amendment Date** **DD Mon YYYY**	**Global/Country/Site-specific** **Global**
Description of Change		**Section(s) Affected by Change**
Not applicable		

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

APPENDIX 3 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

APPENDIX 3.1 REGULATORY AND ETHICAL CONSIDERATIONS

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

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.

APPENDIX 3.2 SPONSOR'S RESPONSIBILITIES

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, current ICH GCP guideline E6 (1996), EU Directive 2001/20/EC Guidelines, 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 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.

Indemnity/Liability and Insurance

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

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.

The timing for study registration and results summary posting(s) must be in accordance with applicable local and national requirements.

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 study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

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.

APPENDIX 3.3 INVESTIGATOR'S RESPONSIBILITIES

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), 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 will be 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).

Protocol Adherence and Investigator Agreement

The investigator and any sub-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.

Documentation and Retention of Records

Case Report Forms

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 relevant 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 CRA/study monitor will verify the CRF contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries will be issued for corrections or verification of data.

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 source documents.

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 the 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.

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.

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).

APPENDIX 3.4 ETHICAL CONSIDERATIONS

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 which was reviewed by the IRB/EC and which 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.

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 the 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.

Investigational product supplied will not be released until the sponsor and/or CRO have received written IRB/EC approval.

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. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol, at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

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

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(s) /EC(s) 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, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, 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.

Study Results / Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites,

whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

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.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Shire is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Shire will require the submission of all Shire-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

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) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

APPENDIX 4 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

APPENDIX 4.1 ADVERSE EVENT DEFINITIONS

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 investigational product or medicinal product. 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).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

Serious Adverse Event

A serious adverse event (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 investigations procedures or 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
- Results in 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 bronchospasm associated with anaphylaxis 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.

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB and/or prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

Suspected adverse reaction

Serious

Unexpected

Assessed as related to study treatment

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing

administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation 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 or expected disease evolution) is found for the abnormal values.

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

APPENDIX 4.2 COLLECTION OF ADVERSE EVENTS

All AEs/SAEs 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.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), 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.

APPENDIX 4.3 ASSESSMENT OF ADVERSE EVENTS

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 is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose of a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

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.

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.

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.

Outcome Categorization

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

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

If applicable, action taken will also be recorded on the AE CRF.

APPENDIX 4.4 SAFETY REPORTING

Reference Safety Information

The reference for safety information for this study is the lanadelumab investigator's brochure version 6.0 which the sponsor has provided under separate cover to all investigators.

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 becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Appendix 4.9) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "Clinical Study Serious Adverse Event for Serious Adverse Events (SAEs) and Non-serious AEs as Required by 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 Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (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.

APPENDIX 4.5 SERIOUS ADVERSE EVENT COLLECTION TIME FRAME

All SAEs (regardless of relationship to investigational product) 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 becoming aware of the event.

APPENDIX 4.6 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 reported 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.

APPENDIX 4.7 FATAL OUTCOME

Any SAE that results in the subject's death (eg, 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 or it is a single dose study). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

APPENDIX 4.8 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 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 and 1 year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the 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.

APPENDIX 4.9 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 Appendix 4.1.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication error s 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 the unassigned treatment is/are always reportable as a medication error.

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 and a protocol deviation.

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.

APPENDIX 4.10 URGENT SAFETY MEASURES

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

APPENDIX 4.11 REGULATORY AGENCY, INSTITUTIONAL REVIEW BOARD, ETHICS COMMITTEE, AND SITE REPORTING

The sponsor and clinical CRO are responsible for notifying the relevant regulatory authorities/US local 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/EC of SAEs or significant safety findings, or the relevant local regulatory authority of all SAEs that occur at his or her site as required by IRB/EC procedures.