PROTOCOL TITLE

A randomized, double-blind, placebo-controlled, phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II

Sponsor:	KalVista Pharmaceuticals, Ltd. Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom
Clinical Research Organization:	Orion Clinical Services Ltd (Orion) 7 Bath Road, Slough Berkshire SL1 3UA United Kingdom
Sponsor Protocol No.:	KVD900-201
IND No.:	143807
EudraCT number:	2018-004489-32
Study Drug Name:	KVD900 100 mg Film Coated Tablet
Development Phase:	2
Date of Protocol:	24 November 2020, Final V5.3 (US only)
Date of Previous Protocol:	24 March 2020, Final V4.3 (US only)

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

SIGNATURE PAGE

Title: A randomized, double-blind, placebo-controlled, phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (2013), and the guidelines on Good Clinical Practice (GCP).

Declaration of the Investigator

Title: A randomized, double-blind, placebo-controlled, phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report form (eCRF), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Independent Ethics Committee (IEC)/ Institutional Review Board (IRB). No substantial changes will be made to the study protocol without the prior written approval of the Sponsor and the IEC/ IRB, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study centre

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

PROTOCOL SYNOPSIS

Title	A randomized, double-blind, placebo-controlled, phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II.
Sponsor Study No.	KVD900-201
Phase	2
Sponsor	KalVista Pharmaceuticals Ltd
Study Centre(s)	Multiple clinical sites in Europe and US
Objectives	Primary Objective: • To investigate the efficacy of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack of hereditary angioedema (HAE). Secondary Objectives: • To investigate the safety and tolerability of KVD900. • To investigate the pharmacokinetic (PK) profile of KVD900 when taken during the intercritical period between HAE attacks. • To investigate the pharmacodynamic (PD) profile of KVD900 in reducing the concentration of residual cleaved high molecular weight kininogen (HK) during the intercritical period between HAE attacks. • To investigate the PD profile of KVD900 in reducing activated plasma enzyme activity during the intercritical period between HAE attacks. Note: Subjects enrolled at US study sites will not contribute data for PK and PD analysis.
Setup	This is a phase 2, two-part, two-sequence, two-period (2x2) cross-over clinical trial: Subjects with HAE type I or II will be recruited through HAE treatment centres in Europe and US. In Part 1, subjects will receive a single oral dose of 600 mg KVD900 to investigate the safety of KVD900 during the intercritical period between HAE attacks. Eligible adult subjects ≥18 years old will undergo a screening assessment for study inclusion, receive study drug, followed by a 4h, in-clinic, safety assessment. In Part 2, the subjects will be randomized 1:1 to 2 treatment sequences. This part of the study will be conducted away from the clinic or hospital. In Sequence 1 (study arm 1) subjects will receive a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a second single dose of placebo to treat the second eligible HAE attack.

In Sequence 2 (study arm 2) subjects will receive a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.

A minimum of 48-hour washout period required between each dose of study drug.

Laryngeal or facial attacks are not eligible for treatment. HAE attacks must be treated within the first hour of onset and before reaching severe on the global attack severity scale. Subjects must also be able to identify the start of a HAE attack. Upon onset of the eligible HAE attack, subjects will notify the dedicated study physician or qualified designee with a description of the HAE attack. The dedicated study physician or qualified designee will confirm eligibility of the HAE attack and agree to study drug being administered. HAE attacks require documentation, on the Subject Diary, of attack location, attack symptoms, time of onset, attack severity, and time of last substantial meal prior to dosing. Subjects will take study drug, as instructed, and will complete timed assessments of their HAE attack symptoms for a 48h period as documented below in Table 1 (S). The dedicated study physician or qualified designee will contact the subject within 24h of the eligible HAE attack to confirm the subject's safety and wellbeing. Subjects will be instructed to contact the dedicated study physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects are to contact the dedicated study physician or qualified designee or contact the nearest emergency service. The dedicated study physician or qualified designee will be available 24h/day and 7 days/week to receive subject calls.

Table 1 (S): Frequency of Subject Assessment

Time Period following Study Drug Administration	Frequency of Subject Assessment*	Allowed Time Window for Assessment
0h – 4h	Every 30 min	None
4h – 12h	Every 1h	+/- 15 min
12h – 24h	Every 3h	+/- 30 min
36h	Once	+/- 60 min
48h	Once	+/- 60 min

In the event that **conventional attack treatment is used, the subject should perform assessments every 30 min for 4 h following first administration of conventional attack treatment. After this, the subject should revert back to original frequency of assessments based on time of study drug administration.*

Subjects will return to the clinic following the first HAE attack, prior to the second HAE attack, to undergo safety checks including adverse event (AE) reporting, vital sign recording, and Subject Diary review.

Once two HAE attacks have been treated in Part 2, the subject will return to the clinic to undergo final safety checks including AE reporting, vital sign recording and blood sampling for laboratory safety measurements.

	Conventional attack treatment is permitted after 4h, or earlier as warranted, following study drug intake, provided HAE attack symptoms are judged severe enough by the subject to require treatment as per the subject's usual treatment regimen, or are deemed ineligible for study drug treatment, or are associated with laryngeal or facial symptoms. Prior to use of conventional attack treatment, subjects will notify the dedicated study physician or qualified designee who will confirm conventional treatment is appropriate per protocol and subject report of symptom severity. Subjects are permitted to treat their HAE attacks with their conventional attack treatment (pdC1INH or rhC1INH intravenous [iv] or icatibant).
Investigational Medicinal Product	KVD900 100 mg Film-Coated Tablet. Placebo to KVD900 100 mg Film-Coated Tablet. No study drug dose modifications are allowed in this study.
Number of Subjects	Approximately 60 subjects will be enrolled into the study to ensure approximately 50 subjects complete the study.
Population	The study population will include male and female subjects 18 years of age or older with HAE type I or II. <u>Inclusion Criteria:</u> 1. Male or female adult subjects 18 years of age and older. 2. Confirmed diagnosis of HAE type I or II at anytime in the medical history: a. Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND b. C1-esterase inhibitor (C1-INH) antigen or functional level < 40% of the normal level. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE type I or II. 3. At least 3 documented HAE attacks in the past 93 days, as supported by medical history. 4. Access to and ability to use conventional attack treatment for attacks of HAE. 5. Adequate organ functions as defined below: a. Hemoglobin within normal range; b. International normalized ratio (INR)< 1.2; c. Activated partial thromboplastin time (aPTT) ≤ upper limit of normal (ULN); d. Creatinine < 1x ULN; e. Creatinine clearance (CrCl) ≥ 60 mL/min; f. Alanine aminotransferase (ALT) ≤ 2x ULN; g. Aspartate aminotransferase (AST) ≤ 2x ULN; h. Total bilirubin ≤ 1.5x ULN;

	i. Leucocytes ≤ 1.5x ULN; j. Thrombocytes ≤ 1.5x ULN. 6. Female of childbearing potential must agree to use highly effective birth control from the Screening visit until the end of the trial follow-up procedures. Highly effective methods of birth control include: a. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral / injectable / implantable. (Hormonal contraception that contains estrogen is excluded per exclusion criterion 3). b. Intrauterine device (IUD). c. Intrauterine hormone–releasing system (IUS). d. Bilateral tubal occlusion. e. Vasectomised partner (provided that the partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomised partner has received medical assessment of the surgical success). f. Sexual abstinence (this method is not acceptable in Switzerland). **Note**: Sexual abstinence will only be considered a highly effective method if it is defined as refraining from heterosexual intercourse. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. 7. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study. 8. Males with female partners of childbearing potential must agree to be abstinent or else use a highly effective method of birth control as defined in inclusion criterion 6 from the Screening visit until the end of the trial follow-up procedures. 9. Provide signed informed consent and are willing and capable of complying with study requirements and procedures.

Exclusion Criteria:

1. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria.
2. Current use of C1INH, androgens, lanadelumab or tranexamic acid for HAE prophylaxis.
3. Use of angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 93 days prior to initial study treatment.
4. Use of androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterones, testosterone) or antifibrinolytics within 30 days prior to initial study treatment.
5. Use of lanadelumab within 10 weeks prior to initial study treatment.
6. Use of strong CYP3A4/CYP2C9 inhibitors and inducers during participation in the trial.

   Note: These medications include but are not limited to the following: cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, boceprevir, telaprevir, troleandomycin, clarithromycin, carbamazepine, enzalutamide, mitotane, phenytoin, phenobarbital, fluconazole, isoniazid, metronidazole, paroxetine, sulfamethoxazole, rifampicin, St. John's Wort, diltiazem, idelalisib, nefazodone and nelfinavir.
7. Clinically significant abnormal electrocardiogram (ECG) at Visit 1 and pre-dose at Visit 2. This includes, but is not limited to, a QTcF > 470 msec (for women) or > 450 msec (for men), a PR > 220 msec or ventricular and/or atrial premature contractions that are more frequent than occasional and/or occur as couplets or higher in grouping.
8. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other cardiovascular abnormality.
9. Any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory, cardiovascular) or significant disease or disorder which, in the opinion of the Investigator, would jeopardize the safety of the subject by taking part in the trial.
10. History of substance abuse or dependence that would interefere with the completion of the study, as determined by the Investigator.
11. Known lactose allergy or intolerance.
12. Known hypersensitivity to KVD900 or placebo or to any of the excipients.
13. Participation in an interventional investigational clinical study within 93 days or within 5 half-lives of the last dosing of investigational drug (whichever is longer) prior to initial study treatment.
14. Any pregnant or breast-feeding subject.

Assessments	Part 1: Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate [PR], respiratory rate [RR] and body temperature) will be measured at pre-dose (0h), 1h, and 4h post-dose. Samples for post-treatment safety laboratory assessments will be taken at 4h post-dose. Part 2: Following study drug intake, subject assessments of overall HAE attack severity and change in HAE attack severity will take place for a 48h period as documented in Table 1 (S). Efficacy Variables: Time to use of conventional attack treatment will be assessed. The subject diary will capture the efficacy endpoints including time to use of conventional attack treatment and HAE attack severity. Overall HAE attack severity will be assessed on the Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS) scored as none, mild, moderate, severe and very severe. Change in HAE attack severity will be assessed using the Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ), scored as Much better / Better / A little better / No change / A little worse / Worse / Much worse. The type of HAE attack symptoms (abdominal pain, skin pain and skin swelling) will each be assessed on a 100 mm visual analogue scale (VAS) anchored at 0 (none) and 100 (very severe). Safety Variables: • AEs, including serious adverse events (SAEs). • Laboratory test results (clinical chemistry, hematology, coagulation, and urinalysis). • Vital signs (SBP, DBP, PR, RR, body temperature). • Physical examination findings. • ECG results. • Pregnancy test (female subjects of child-bearing potential).

Criteria for Evaluation of Efficacy	Primary Efficacy Endpoints:
	• Time to use of conventional attack treatment within 12h of study drug.
	Secondary Efficacy Endpoints:
	• PGI-S (5LS)
	  ○ Worsening (including use of conventional attack treatment)
	  • Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use conventional attack treatment within 12h of study drug
	  • Time to (1) worsening by one level or more from baseline, or (2) use of conventional attack treatment, whichever comes first within 12h of study drug
	• PGI-C (7TQ)
	  ○ Improvement
	  • Time to symptom relief (*A little better* or higher, 2 time points in a row) within 12h of study drug

	• Visual Analogue Scale (VAS)
	  ○ Improvement
	  • Time to symptom relief (50% reduction from baseline in composite VAS, 3 time points in a row) within 12h of study drug.
	<u>Exploratory Endpoints:</u>
	• Use of Conventional Treatment
	  ○ Proportion of HAE attacks that require conventional attack treatment within 12h and 24h of study drug
	  ○ Time to use of conventional attack treatment within 24h of study drug
	• PGI-S (5LS)
	  ○ Area Under the Curve (AUC)
	  • Cumulative PGI-S (5LS) expressed as AUC within 12h and 24h of study drug
	  ○ Worsening (including use of conventional attack treatment)
	  • Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 24h of study drug
	  • Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 24h of study drug
	  ○ Worsening Only
	  • Time to worsening by one level or more from baseline within 12h and 24h of study drug
	  ○ Improvement
	  • Proportion of HAE attacks that improve by one level or more from baseline within 12h and 24h of study drug
	  • Time to improvement by one level or more from baseline within 12h and 24h of study drug
	  • Proportion of subjects with HAE attack resolution (rating of *none*) within 12h and 24h of study drug
	  • Time to HAE attack resolution (rating of *none*) within 12h and 24h of study drug
	  ○ Stable or Improvement
	  • Proportion of HAE attacks that are stable or improved from baseline within 12h and 24h of study drug
	• PGI-C (7TQ)
	  ○ AUC
	  • Cumulative PGI-C (7TQ) expressed as AUC within 12h and 24h of study drug
	  ○ Worsening (including use of conventional attack treatment)

	• Proportion of HAE attacks that are (1) rated *A little worse* or higher, 2 time points in a row or (2) use of conventional attack treatment within 12h and 24h of study drug • Time to HAE attack being (1) rated *A little worse* or higher, 2 time points in a row, or (2) use of conventional attack treatment, whichever comes first, within 12h and 24h of study drug o Worsening Only • Time to HAE attack being rated *A little worse* or higher, 2 time points in a row, within 12h and 24h of study drug o Improvement • Proportion of HAE attacks that are rated *A little better* or higher, 2 time points in a row, within 12h and 24h of study drug • Time to HAE attack being rated *A little better* or higher, 2 time points in a row, within 24h of study drug • Proportion of HAE attacks that are rated *Better* or higher within 12h and 24h of study drug • Time to HAE attack being rated *Better* or higher within 12h and 24h of study drug o Stable or Improvement • Proportion of HAE attacks that are stable or improved within 12h and 24h of study drug • Visual Analogue Scale (VAS) o AUC • Cumulative composite VAS expressed as AUC within 12h and 24h of study drug o Improvement • Proportion of HAE attacks with symptom relief (50% reduction from baseline in composite VAS, 3 time points in a row) within 12h and 24h of study drug • Time to symptom relief (50% reduction in composite VAS, 3 time points in a row) within 24h of study drug
General Statistical Methods and Types of Analyses	Analysis Sets: • Safety set (SAF): Subjects who have taken at least one dose of study drug (including the study drug dose in Part 1). • Full analysis set (for efficacy) (FAS): All randomized subjects who received both doses of study drug in Part 2. • Per protocol set (for efficacy) (PPS): Randomized subjects in Part 2 who received KVD900 both doses of study drug in Part 2 and have no major protocol deviations. • PK / PD analysis set: All subjects for whom PK / PD samples were taken in Part 1. (Note: Subjects enrolled at US study sites will not contribute data for PK and PD analysis.)

	Sample Size: A sample size of approximately 50 subjects (25 per sequence) is proposed to provide 90% power for testing at the 5% alpha level (2-sided) for the primary endpoint of time to use of conventional attack treatment within 12h of study drug. [redacted] The assumption of minimal correlation should be a conservative assumption with respect to sample size. Approximately 60 subjects will be enrolled to ensure that approximately 50 subjects complete the study. An oversampling by 20% (10 subjects) is proposed to account for subjects that may not complete both treatment periods due to infrequent or ineligible HAE attacks or for subjects who discontinue the trial early, for whatever reason. Thus, study enrolment will be considered sufficient to address the primary efficacy hypothesis after approximately 50 subjects have completed both treatment periods. Since further exposure is not required and could be considered unnecessary, ongoing subjects who have not completed both periods will be asked to return to the study site and complete Visit 4 (Early Discontinuation visit). Data from all subjects, complete and incomplete, will be analyzed in the safety set. General Considerations: Individual subject data will be presented in subject data listings. Appropriate descriptive statistics will be calculated for continuous and categorical data and summarized in tabular format. Safety Analyses: AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (v21.0 or higher) and classified by preferred term and system organ class (SOC). Listings of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group, and further classified by TEAE severity and relationship to study drug. Efficacy Analyses: *Primary Endpoint* The primary endpoint, time to use of conventional attack treatment within 12h of study drug, [redacted] to reflect the repeat measures on each subject. Subjects will be treated as censored if conventional attack treatment is not used within 12h of study drug administration. *Secondary Endpoints* For comparisons of proportions [redacted] will be used to compare the treatment arms. Secondary and exploratory endpoints, using *time to event* as the unit of analysis, will be analyzed using a similar approach to that used for the primary endpoint.

	Note: Subjects enrolled at US study sites will not contribute data for PK and PD analysis. PK Analysis: Non-compartmental PK parameters will include, but are not limited to, maximum concentration in plasma (C_{max}), time to reach C_{max} in plasma (t_{max}), area under the curve from time 0 to last measurable concentration (AUC_{0-t}), apparent clearance (CL/F), apparent volume of distribution (Vd/F) and estimated terminal elimination half-life ($t_{½}$). The PK parameters of KVD900 will be determined from the individual concentration versus time data using Phoenix WinNonlin. In case of a deviation from the theoretical time, the actual time of blood sample will be used in the calculation of the derived PK parameters. Individual concentrations and derived PK parameters of KVD900 in plasma will be listed and summarized for each treatment. Individual and geometric mean concentration-time data will be plotted on linear and semi-logarithmic scales. PD Analysis: KVD900's effect on plasma kallikrein (PKa) activity will be analyzed using two exploratory measures of PKa enzyme activity in plasma: • An assay to determine inhibition of exogenously activated plasma kallikrein enzyme activity from plasma samples obtained before and after receiving KVD900. • An assay to measure the level of protection of cleavage of high molecular weight kininogen (HK) substrate (contained in whole plasma) from plasma kallikrein enzyme activity. The PD will be summarized for each treatment. Individual and mean data will be provided as a report addendum located in the appendix of the final Clinical Study Report.

LIST OF STUDY PERSONNEL

Sponsor	KalVista Pharmaceuticals, Ltd. Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom [redacted]
Contract Research Organization and Medical Monitoring	Orion Clinical Services Ltd (Orion) 7 Bath Road, Slough Berkshire SL1 3UA United Kingdom [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5LS	5-point Likert scale
7TQ	7-point transition question
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	area under the curve from time 0 to last sample
BMI	body mass index
C1-INH	C1-esterase inhibitor
CL/F	apparent clearance
C_{max}	maximum concentration in plasma
CRA	Clinical Research Associate
CrCl	creatinine clearance
DBP	diastolic blood pressure
DRL	Drug Reference List
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data collection
FAS	full analysis set
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
H	hour(s)
HAE	hereditary angioedema
HgA1c	glycosylated hemoglobin
HK	high molecular weight kininogen
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization
ID	Identification

IEC	Independent Ethics Committee
INR	international normalized ratio
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone–releasing system
Iv	Intravenous
Kg	kilogram(s)
M	meter(s)
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mL	Milliliter(s)
NOAEL	No-observed Adverse Effect Level
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PD	Pharmacodynamic
pH	potential hydrogen
PK	Pharmacokinetic
PKa	plasma kallikrein
PPS	per protocol set
PR	pulse rate
PT	prothrombin time
PV	Pharmacovigilance
QP	Qualified Person
RR	respiratory rate
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class

SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	estimated terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max} in plasma
ULN	upper limit of normal
VAS	visual analogue scale
Vd/F	apparent volume of distribution
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND

Hereditary angioedema (HAE) is a rare genetic disease characterized by repeated episodes of non-pitting edema that can affect any cutaneous or mucosal surface. Swelling of the face, larynx, tongue, extremities, stomach, bowels, and genitals is common and can be associated with significant morbidity and mortality. The most common form of HAE is autosomal dominant and results from a loss-of-function mutation in the gene that codes for C1 inhibitor protein. Under normal circumstances, a functional level of C1 inhibitor in plasma prevents over-activation of the complement system and over-production of the vasoactive mediator, bradykinin. Deficiency of C1 inhibitor allows for excessive release of bradykinin and complement anaphylatoxins, which results in increased endothelial permeability and edema (*Kaplan and Joseph, 2017*).

1.1 Rationale for the Study

Bradykinin is formed by the action of a protease enzyme, plasma kallikrein (PKa), on a precursor molecule, kininogen, leading to the release of active bradykinin into the circulation. In the absence of C1 inhibitor (as is the case in HAE), excessive bradykinin activity triggers the HAE attacks. It is therefore logical to target PKa as a treatment strategy in HAE.

[redacted]

It is therefore a plausible hypothesis that treatment with a single dose of KVD900 600 mg may halt the progression of HAE attacks.

Refer to the Investigator's Brochure (IB) for further detail on KVD900.

1.2 Benefit Risk Assessment

In contrast to other available on-demand treatments for HAE attacks, KVD900 is orally-administered, is rapidly absorbed from the tablet formulation and has been shown in healthy volunteers to have a time profile for kallikrein inhibition [redacted] which is appropriate for the treatment of this condition. A single dose of 600 mg may be reasonably expected to bring relief to or halt the progression of an attack of HAE. The double-blind, placebo-controlled crossover design of Part 2 of the study has been chosen as an appropriate initial test of that hypothesis.

[redacted]

[redacted]

The two-part design of the current study has been chosen in order to confirm under open-label, clinic-supervised conditions (Part 1) that administration of a single 600 mg dose of KVD900 is tolerated by individual subjects before that dose is administered away from the clinic or hospital in Part 2 of the study. Further safety features of Part 2 include the exclusion of laryngeal or facial attacks and the availability of conventional attack treatment from 4h after study treatment, or earlier, as warranted.

Overall, study KVD900-201 is considered to have a positive benefit-risk balance given that:

- Inhibition of plasma kallikrein is not a novel mechanism for the treatment of HAE. There are currently approved plasma kallikrein inhibitors that do not have known target-related AEs.
- [redacted]
- The initial dose of KVD900 600 mg will be taken in the clinic under the supervision of the Investigator.
- The dose of KVD900 to be taken in Part 2 (away from the clinic or hospital) will only be taken once a study physician or qualified designee has confirmed the HAE attack to be eligible and, importantly, that it is not a laryngeal or facial attack. In this case, subjects will treat immediately with their conventional attack treatment (pdC1INH or rhC1INH intravenous [iv] or icatibant). The dedicated study physician or qualified designee will also contact the subject within 24h of the eligible HAE attack to confirm the subject's safety and wellbeing. Subjects will be instructed to contact the dedicated study physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects are to contact the dedicated study physician or qualified designee or contact the nearest emergency service. The dedicated study physician or qualified designee will be available 24h/day and 7 days/week to receive subject calls.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To investigate the efficacy of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack of HAE.

2.2 Secondary Objective(s)

- To investigate the safety and tolerability of KVD900.
- To investigate the pharmacokinetic (PK) profile of KVD900 when taken during the intercritical period between HAE attacks.
- To investigate the pharmacodynamic (PD) profile of KVD900 in reducing the concentration of residual cleaved high molecular weight kininogen (HK) during the intercritical period between HAE attacks.
- To investigate the PD profile of KVD900 in reducing activated plasma enzyme activity during the intercritical period between HAE attacks.

Note: Subjects enrolled at US study sites will not contribute data for PK and PD analysis.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a phase 2, randomized, two-part, two-sequence, two-period (2x2) cross-over clinical trial to evaluate the efficacy, safety, and tolerability of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack in adult subjects with HAE type I or II. Approximately 60 subjects will be enrolled into the study to ensure approximately 50 subjects complete the study.

The study will be in two parts with the same cohort of subjects completing both parts (Figure 1).

In Part 1, subjects will receive a single oral dose of 600 mg KVD900 to investigate the safety of KVD900 during the intercritical period between HAE attacks. Eligible adult subjects ≥18 years old will undergo a screening assessment for study inclusion, receive study drug, followed by a 4h, in-clinic, safety assessment.

In Part 2, the subjects will be randomized 1:1 to 2 treatment sequences. This part of the study will occur away from the clinic or hospital.

In Sequence 1 (study arm 1) subjects will receive a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a second single dose of placebo to treat the second eligible HAE attack.

In Sequence 2 (study arm 2) subjects will receive a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.

The final clinic visit will take place once both eligible HAE attacks have been treated.

The maximum duration of the study for each randomized subject is likely to be approximately 19 weeks.

The study schedule of events will be as follows:

Screening Phase (Visit 1): The screening period will be up to 28 days. All subjects will sign an Informed Consent Form (ICF) prior to any study related procedures being performed. Subjects will be 18 years of age or older, at the time of screening, and will have a diagnosis of HAE type I or II.

Part 1 (Visit 2): On the day of first study drug administration the subject's eligibility will be reconfirmed and baseline assessments will be performed. Eligible subjects will receive a single oral dose of KVD900 600 mg. Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate [PR], respiratory rate [RR] and body temperature) will be measured at pre-dose (0h), 1h, and 4h post-dose. Samples for post-treatment safety laboratory assessments will be taken at 4h post-dose.

Part 2: This will be conducted away from the clinic or hospital. Laryngeal or facial attacks are not eligible for treatment. Eligible HAE attacks must be treated within the first hour of onset and before reaching severe on the global attack severity scale. Subjects must also be able to identify the start of an HAE attack. Upon onset of the HAE attack, subjects will notify the dedicated study physician or qualified designee with a description of the HAE attack symptoms. The dedicated study physician or qualified designee will confirm eligibility of the HAE attack and agree to study drug being administered. HAE attacks require documentation, on the Subject Diary, of attack location, attack symptoms, time of onset, attack severity, and time of last substantial meal prior to dosing prior to dosing. Subjects will take study drug, as instructed, and will complete timed assessments of their HAE attack symptoms for a 48h period following study

drug intake as documented in Table 2. The dedicated study physician or qualified designee will contact the subject within 24h of the eligible HAE attack to confirm the subject's safety and wellbeing. Subjects will be instructed to contact the dedicated study physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects are to contact the dedicated study physician or qualified designee or contact the nearest emergency service. The dedicated study physician or qualified designee will be available 24h/day and 7 days/week to receive subject calls.

Subjects will return to the clinic (***Visit 3***) following the first eligible HAE attack, prior to the second eligible HAE attack, to undergo safety checks including AE reporting, vital sign recording, and Subject Diary review.

End of study visit (Visit 4): Once two eligible HAE attacks have been treated in Part 2, the subject will return to the clinic to undergo final safety checks including AE reporting, vital sign recording and blood sampling for laboratory safety measurements.

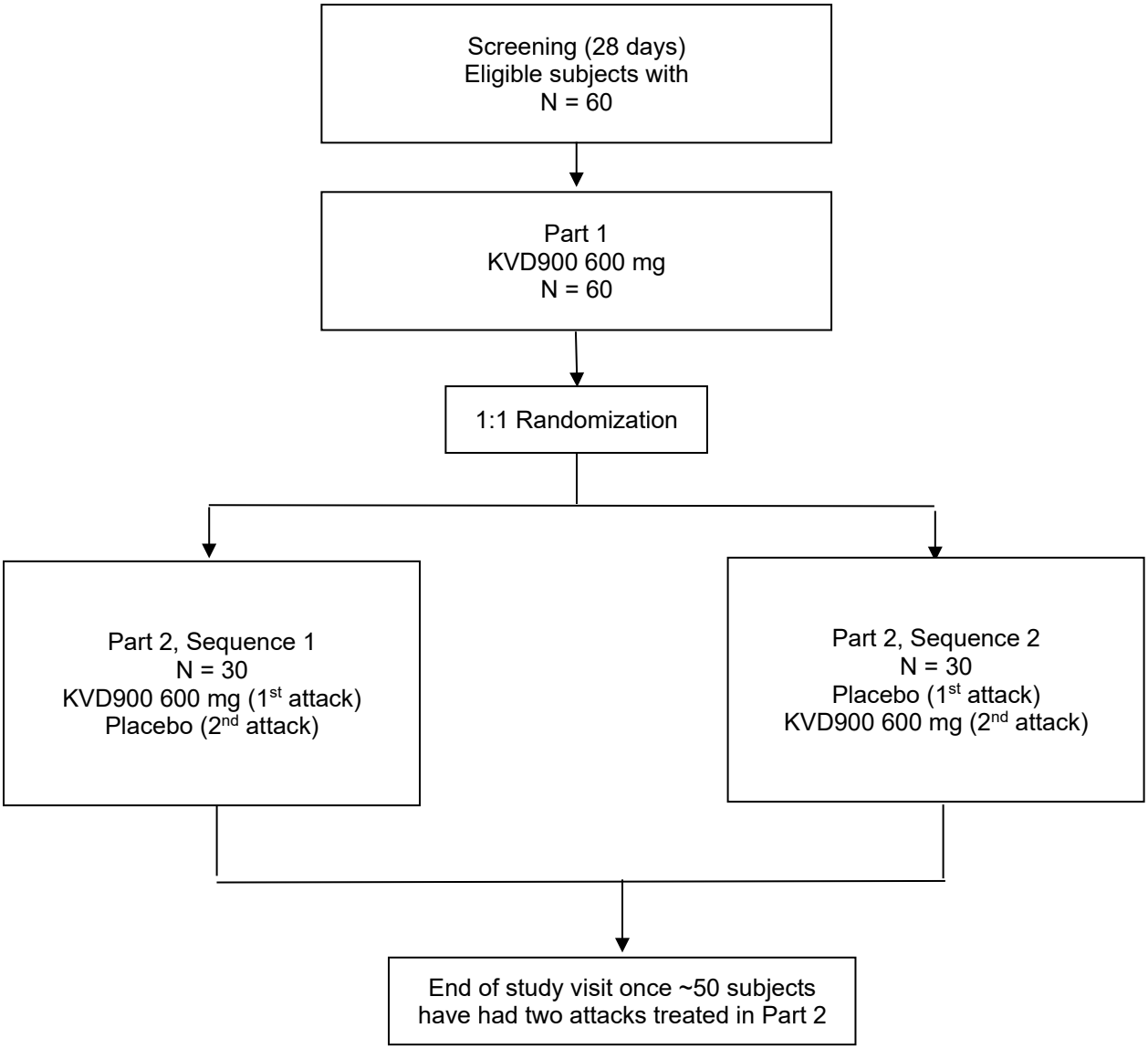
Early Discontinuation: If any subject discontinues the trial early, (i.e. before having treated two eligible HAE attacks within Part 2) every effort should be made to complete Visit 4 (Early Discontinuation visit) as soon as possible and, whenever possible, prior to starting any new medication or treatment. All attempts will be made to avoid early discontinuation

***Study Termination*:** A sample size of approximately 50 subjects completing both treatment periods (25 per sequence) is proposed to provide 90% power for testing at the 5% alpha level (2-sided) for the primary endpoint of time to use of conventional attack treatment within 12h of study drug. [redacted]
The assumption of minimal correlation should be a conservative assumption with respect to sample size.

An oversampling by 20% (10 subjects) is proposed to account for subjects that may not complete both treatment periods due to infrequent or ineligible HAE attacks or for subjects who discontinue the trial early, for whatever reason. Thus, study enrolment will be considered sufficient to address the primary efficacy hypothesis after approximately 50 subjects have completed both treatment periods. Since further exposure is not required and could be considered unnecessary, ongoing subjects who have not completed both periods will be asked to return to the study site and complete Visit 4 (Early Discontinuation visit). Data from all subjects, complete and incomplete, will be analyzed in the safety set.

Conventional Attack Treatment: Conventional attack treatment is permitted after 4h, or earlier as warranted, following study drug intake, provided HAE attack symptoms are judged severe enough by the subject to require treatment as per the subject's usual treatment regimen, or are associated with laryngeal or facial symptoms. Prior to use of conventional attack treatment, subjects will notify the dedicated study physician or qualified designee who will confirm conventional attack treatment is appropriate per protocol and subject report of symptom severity. Subjects are permitted to treat their HAE attacks with their conventional attack treatment (pdC1INH or rhC1INH iv or icatibant).

Figure 1: Study Flow Chart



3.2 Criteria for Evaluation of the Study

3.2.1 Efficacy Endpoints

3.2.1.1 Primary Efficacy Endpoints

- Time to use of conventional attack treatment within 12h of study drug.

3.2.1.2 Secondary Efficacy Endpoints

- Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS):
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use conventional attack treatment within 12h of study drug.
    - Time to (1) worsening by one level or more from baseline, or (2) use of conventional attack treatment, whichever comes first within 12h of study drug.
- Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ):
  - Improvement:
    - Time to symptom relief (*A little better* or higher, 2 time points in a row) within 12h of study drug.
- Visual Analogue Scale (VAS):
  - Improvement:
    - Time to symptom relief (50% reduction from baseline in composite VAS, 3 time points in a row) within 12h of study drug.

3.2.1.3 Exploratory Endpoints

- Use of Conventional Treatment:
  - Proportion of HAE attacks that require conventional attack treatment within 12h and 24h of study drug.
  - Time to use of conventional attack treatment within 24h of study drug.
- PGI-S (5LS):
  - Area Under the Curve (AUC):
    - Cumulative PGI-S (5LS) expressed as AUC within 12h and 24h of study drug.
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 24h of study drug.
    - Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 24h of study drug.

- Worsening Only:
  - Time to worsening by one level or more from baseline within 12h and 24h of study drug.
- Improvement:
  - Proportion of HAE attacks that improve by one level or more from baseline within 12h and 24h of study drug.
  - Time to improvement by one level or more from baseline within 12h and 24h of study drug.
  - Proportion of subjects with HAE attack resolution (rating of *none*) within 12h and 24h of study drug.
  - Time to HAE attack resolution (rating of *none*) within 12h and 24h of study drug.
- Stable or Improvement:
  - Proportion of HAE attacks that are stable or improved from baseline within 12h and 24h of study drug.

- PGI-C (7TQ):
  - AUC:
    - Cumulative PGI-C (7TQ) expressed as AUC within 12h and 24h of study drug.
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that are (1) rated *A little worse* or higher, 2 time points in a row or (2) use of conventional attack treatment within 12h and 24h of study drug.
    - Time to HAE attack being (1) rated *A little worse* or higher, 2 time points in a row, or (2) use of conventional attack treatment, whichever comes first, within 12h and 24h of study drug.
  - Worsening Only:
    - Time to HAE attack being rated *A little worse* or higher, 2 time points in a row, within 12h and 24h of study drug.
  - Improvement:
    - Proportion of HAE attacks that are rated *A little better* or higher, 2 time points in a row, within 12h and 24h of study drug.
    - Time to HAE attack being rated *A little better* or higher, 2 time points in a row, within 24h of study drug.
    - Proportion of HAE attacks that are rated *Better* or higher within 12h and 24h of study drug.
    - Time to HAE attack being rated *Better* or higher within 12h and 24h of study drug.

- Stable or Improvement:
  - Proportion of HAE attacks that are stable or improved within 12h and 24h of study drug.

- Visual Analogue Scale (VAS):
  - AUC:
    - Cumulative composite VAS expressed as AUC within 12h and 24h of study drug.
  - Improvement:
    - Proportion of HAE attacks with symptom relief (50% reduction from baseline in composite VAS, 3 time points in a row) within 12h and 24h of study drug.
    - Time to symptom relief (50% reduction in composite VAS, 3 time points in a row) within 24h of study drug.

3.2.2 Safety Endpoints

- AEs, including SAEs.
- Physical exam findings.
- Electrocardiogram (ECG) results.
- Laboratory test results (clinical chemistry, hematology, coagulation, and urinalysis).
- Vital signs (SBP, DBP, PR, RR and body temperature).

3.3 Justification of the Study Design

This phase 2 study is the first clinical investigation of the potential efficacy of KVD900 in the on-demand treatment of attacks of HAE. The two-part design has been chosen to allow preliminary assessment of the safety and tolerability of the drug in this population between HAE attacks and in a controlled clinic environment before moving on to compare efficacy against placebo in peripheral or abdominal attacks away from the clinic or hospital. Laryngeal and facial attacks are excluded for safety reasons at this early stage of development.

The study population is representative of the likely target population for the product. The analysis sample size of approximately 50 subjects is required to conclusively evaluate a clinically relevant treatment effect. Approximately 60 subjects will be enrolled into the study to ensure a total of approximately 50 subjects complete the study.

The single oral 600 mg dose of KVD900 is supported by animal toxicology data and was shown in the first-in-man study to be well tolerated and to result in potentially beneficial PD effects.

The endpoints are commonly-measured in HAE and are clinically relevant.

4 STUDY POPULATION

The study population will include male and female subjects 18 years of age or older with HAE type I or II.

Subjects must fulfill all of the following criteria both at Visit 1 (Screening) and on Visit 2 to be eligible for inclusion in the study.

4.1 Inclusion Criteria

Subject must fulfill all of the following inclusion criteria at Visit 1 (Screening) and on Visit 2 to be eligible for inclusion in the study:

1. Male or female adult subjects 18 years of age and older.
2. Confirmed diagnosis of HAE type I or II at anytime in the medical history:
    a) Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND
    b) C1-esterase inhibitor (C1-INH) antigen or functional level < 40% of the normal level. Subjects with antigen or functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range and a family history consistent with HAE type I or II.
3. At least 3 documented HAE attacks in the past 93 days, as supported by medical history.
4. Access to and ability to use conventional attack treatment for attacks of HAE.
5. Adequate organ functions as defined below:
    a) Hemoglobin within normal range;
    b) International normalized ratio (INR)< 1.2;
    c) Activated partial thromboplastin time (aPTT) ≤ upper limit of normal (ULN);
    d) Creatinine < 1x ULN;
    e) Creatinine clearance (CrCl) ≥ 60 mL/min;
    f) Alanine aminotransferase (ALT) ≤ 2x ULN;
    g) Aspartate aminotransferase (AST) ≤ 2x ULN;
    h) Total bilirubin ≤ 1.5x ULN;
    i) Leucocytes ≤ 1.5x ULN;
    j) Thrombocytes ≤ 1.5x ULN.
6. Females of childbearing potential must agree to use highly effective birth control from the Screening visit until the end of the trial follow-up procedures.

    Highly effective methods of birth control include:

    - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral / injectable / implantable. (Hormonal contraception that contains estrogen is excluded per exclusion criterion 3).
    - Intrauterine device (IUD).

- Intrauterine hormone–releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomised partner (provided that the partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomised partner has received medical assessment of the surgical success).
- Sexual abstinence (this method is not acceptable in Switzerland).

  Note: Sexual abstinence will only be considered a highly effective method if it is defined as refraining from heterosexual intercourse. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

7. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months, do not require contraception during the study.
8. Males with female partners of childbearing potential must agree to be abstinent or else use a highly effective method of birth control as defined in inclusion 6 from the Screening visit until the end of the trial follow-up procedures.
9. Provide signed informed consent and are willing and capable of complying with study requirements and procedures.

4.2 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following statements are applicable at Screening (Visit 1) and on Visit 2:

1. Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (also known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria.
2. Current use of C1INH, androgens, lanadelumab, or tranexamic acid for HAE prophylaxis.
3. Use of angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 93 days prior to initial study treatment.
4. Use of androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterones, testosterone) or antifibrinolytics within 30 days prior to initial study treatment.
5. Use of lanadelumab within 10 weeks prior to initial study treatment.
6. Use of strong CYP3A4/CYP2C9 inhibitors and inducers during participation in the trial.

   Note: These medications include but are not limited to the following: cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, boceprevir, telaprevir, troleandomycin, clarithromycin, carbamazepine, enzalutamide, mitotane, phenytoin, phenobarbital, fluconazole, isoniazid, metronidazole, paroxetine, sulfamethoxazole, rifampicin, St. John's Wort, diltiazem, idelalisib, nefazodone and nelfinavir.
7. Clinically significant abnormal ECG at Visit 1 and pre-dose at Visit 2. This includes, but is not limited to, a QTcF > 470 msec (for women) or > 450 msec (for men), a PR > 220 msec or ventricular and/or atrial premature contractions that are more frequent than occasional and/or occur as couplets or higher in grouping.

8. Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other cardiovascular abnormality.
9. Any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory, cardiovascular) or significant disease or disorder which, in the opinion of the Investigator, would jeopardize the safety of the subject by taking part in the trial.
10. History of substance abuse or dependence that would interefere with the completion of the study, as determined by the Investigator.
11. Known lactose allergy or intolerance.
12. Known hypersensitivity to KVD900 or placebo or to any of the excipients.
13. Participation in an interventional investigational clinical study within 93 days or within 5 half-lives of the last dosing of investigational drug (whichever is longer) prior to initial study treatment.
14. Any pregnant or breast-feeding subject.

4.3 Subject Withdrawal

4.3.1 Withdrawal from Study

Subjects are free to withdraw from participation in the study at any time, for any reason (or without providing reasons) and without prejudice to further treatment or they may be discontinued by the Investigator, if deemed in their best medical interests.

Subjects will also be withdrawn if the entire study is terminated prematurely as described in Section 9.10.

The Sponsor has the right to terminate the study at any time and for any reason. In the event, the Investigators will be informed of the reason for study termination by written notification.

A sample size of approximately 50 subjects completing both treatment periods (25 per sequence) is proposed to provide 90% power for testing at the 5% alpha level (2-sided) for the primary endpoint of time to use of conventional attack treatment within 12h of study drug. [redacted] The assumption of minimal correlation should be a conservative assumption with respect to sample size.

An oversampling by 20% (10 subjects) is proposed to account for subjects that may not complete both treatment periods due to infrequent or ineligible HAE attacks or for subjects who discontinue the trial early, for whatever reason. Thus, study enrolment will be considered sufficient to address the primary efficacy hypothesis after approximately 50 subjects have completed both treatment periods. Since further exposure is not required and could be considered unnecessary, ongoing subjects who have not completed both periods will be asked to return to the study site and complete Visit 4 (Early Discontinuation visit). Data from all subjects, complete and incomplete, will be analyzed in the safety set.

4.3.2 Withdrawal from Treatment

Subjects have the right to stop study treatment at any time, without prejudice to their medical care.

The Investigator may also discontinue a subject from further study drug dosing or withdraw a subject from the study at any time for the following reasons:

- ALT or AST > 8x ULN.
- ALT or AST > 5x ULN for more than 2 weeks.
- ALT or AST > 3x ULN and (total bilirubin > 2x ULN or INR > 1.5).
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Creatinine level increase of > 0.3 mg/dL or creatinine 2.0x baseline value.
- Positive pregnancy test.
- AEs, SAEs.
- At the discretion of the Investigator.
- Administrative reasons (e.g., lack of subject compliance to study visits / procedures, lost to follow-up).

4.3.3 Lost to Follow-up

If a subject does not return for a scheduled visit, every effort should be made at least once every month to contact the subject to reschedule the visit. All efforts should be documented in the subject's medical source record. A subject is considered lost to follow–up if subject cannot be reached after 93 days from the scheduled visit. However, if the subject re–initiates contact beyond 93 days, the available data may still be collected on the electronic case report form (eCRF), provided that subject consent has not been withdrawn.

4.3.4 Withdrawal Procedures

Subjects who withdraw or are withdrawn from the study will complete Visit 4 as soon as possible (Section 7.2.4). The reason for discontinuation / withdrawal will be documented in the eCRF and the Medical Monitor must be informed immediately. If the reason for withdrawal is the occurrence of an AE, the subject will be followed up until the AE has resolved or is considered chronic and stable or the AE has been clearly shown to be unrelated to the study drug.

Withdrawn subjects will not be replaced; screening / randomization codes of withdrawn subjects will not be reused.

4.4 Planned Sample Size and Number of Study Centres

Multiple clinical sites in Europe and US will enroll approximately 60 subjects into the study. Only study sites with experience in the conduct of HAE clinical studies will be selected. See Section 8.9 for a discussion of sample size.

4.5 Subject Identification and Randomization

4.5.1 Subject Identification

Each subject will receive a unique screening identification (ID) number. Subjects who are screen failures and are not randomized will retain their screening ID number.

4.5.2 Randomization Scheme

Subjects will be randomized on a 1:1 basis to the two sequences for Part 2 (KVD900 600 mg followed by placebo or placebo followed by KVD900 600 mg).

4.5.3 Allocation / Randomization of Subjects to Treatment

Subjects must not be randomized unless all eligibility criteria have been met.

Subjects who satisfy all the entry criteria will be assigned to a treatment sequence according to the randomization scheme. Each randomized subject will receive a unique randomization number. Subjects will be randomized in a 1:1 ratio to Sequence 1 (KVD900 followed by placebo) or Sequence 2 (placebo followed by KVD900).

The actual treatment sequence for each subject will be determined by the randomization scheme. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.

The randomization scheme will inform the Investigator of the kit ID number to be allocated to the subject.

The first dose of study drug will be the open label single 600 mg oral dose comprised of 6 x KVD900 100 mg Film Coated Tablets administered in the clinic during Part 1, after completion of all pre–dose assessments.

Randomized subjects who are discontinued (Section 4.3) from further study drug administration or are terminated from the study for any reason, regardless of whether study drug was taken or not, will not have their screening / randomization code be reused.

5 STUDY DRUG

5.1 Identity

[redacted]

Further information about KVD900 100 mg Film-Coated Tablet can be found in the IB.

5.2 Administration

A single open-label dose of KVD900 600 mg (6 x 100 mg tablets) will be administered under the supervision of the clinic staff in Part 1.

In Part 2 each subject, having contacted the dedicated study physician or qualified designee with a description of the HAE attack symptoms and obtained the dedicated study physician or qualified designee's confirmation of HAE attack eligibility and agreement to use study drug, will self-administer a single dose of KVD900 600 mg (6 x 100 mg tablets) or matching placebo tablets in response to the first qualifying attack of HAE.

Subjects will return to the clinic following the first eligible HAE attack and will be dispensed the opposite study drug to take home for treatment of the second eligible HAE attack.

Note: A minimum of 48-hour washout period required between each dose of study drug. Refer also to Section 5.8 for the required washout period prior to dosing with the study drug in the event a subject receives treatment with C1INH or icatibant (all doses) during the study.

Subjects will be provided with instructions on study drug administration and the relevant documentation thereof in the Subject Diary.

No study drug dose modifications are allowed in this study.

5.3 Packaging, Labelling and Storage

[redacted]

5.4 Blinding and Breaking the Blind

Part 2 of the study will be performed in a double–blind manner.

The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement[1] (e.g., for SAEs or death). The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded. The decision to break the study blind will be made solely by the Investigator.

Before breaking the blind of an individual subject's treatment, the Investigator should determine that the unblinded information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the study drug, the problem may be properly managed by assuming that the subject is receiving active product.

Following the unblinding of the study drug for a subject, the Investigator should inform the Sponsor and Medical Monitor. In addition to this, the date, time, and reason for unblinding must be recorded in the subject's eCRF system, and any associated AE report.

If an Investigator, site personnel performing assessments, or subject, is unblinded, the subject must be listed as major protocol deviation.

Suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the Regulatory Authorities.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered onto the database and all data queries have been resolved, and the assignment of subject to the analysis sets has been completed.

5.5 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

The Investigator or designee is responsible for verifying accurate delivery of the study drug and acknowledging receipt thereof by completing and processing the relevant accompanying documentation as required. A copy will be retained for the Investigator Site File.

The Investigator or designee will maintain accountability records that must document all study drug received from the Sponsor, dispensed (as per the protocol / amendment[s]) to the subjects, returned by the subjects, and returned to the Sponsor or sent for destruction (following Sponsor approval). In addition to this, the accountability records will document any additional relevant information received by the Investigator or Pharmacist.

Records should include dates, quantities, batch numbers, expiration dates, and any unique code numbers assigned to the study drug and / or subjects.

The Investigator or designee will dispense the study drug only to the identified subjects of this study following the procedures described in this study protocol and documented in the subject dispensing log.

[1] *The study team (Sponsor and Orion) and Investigator are not unblinded for the purposes of regulatory reporting.*

Study drug inventory / dispensing will be documented in the source documentation and the eCRF for each subject. The Investigator is responsible for all study drug. Written documentation is mandatory.

Subjects will be instructed to return all unused study drug and packaging to the clinic at their subsequent visits (Visits 3 and 4).

All drug accountability forms will be routinely reviewed by the Orion Clinical Research Associate (CRA).

The site staff should aim to follow up on the reasons for any missing study drug or other discrepancies noted after performing the relevant study drug accountability.

Study drug that has been dispensed to a subject and returned unused must not be re-dispensed for a different subject. Unused study drug must not be used for any purpose other than the present study.

After completion of the study and following Sponsor approval, all unused study drug will either be returned to the Sponsor or sent for destruction within 8 weeks of the last dose.

5.6 Compliance

In Part 1, study drug administration and dispensing procedures shall be conducted by qualified staff at the clinical site; study drug administration must be recorded in the source data and eCRF.

In Part 2, subjects will be provided with instructions on study drug administration and the relevant documentation thereof in the Subject Diary. Subjects will also be instructed to return all used and unused study drug and packaging to the clinic at their subsequent visits (Visits 3 and 4).

5.7 Concomitant Medications / Therapy

The concomitant use of the following medications will not be allowed in the study:

- Conventional attack treatment during 4h following study drug intake in Part 2 unless clinically necessary. (Conventional attack treatment is permitted after 4 h or earlier as warranted, as described in Section 5.8.)
- Use of ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 93 days prior to initial study treatment.
- Use of androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) or antifibrinolytics within 30 days prior to initial study treatment.
- Use of lanadelumab within 10 weeks prior to initial study treatment.
- Use of strong CYP3A4/CYP2C9 inhibitors and inducers during participation in the trial.
    - These medications include but are not limited to the following: cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, boceprevir, telaprevir, troleandomycin, clarithromycin, carbamazepine, enzalutamide, mitotane, phenytoin, phenobarbital, fluconazole, isoniazid, metronidazole, paroxetine, sulfamethoxazole, rifampicin, St. John's Wort, diltiazem, idelalisib, nefazodone and nelfinavir.

- Any medication that in the opinion of the Investigator may influence the interpretation of the safety and / or efficacy parameters in this study.

Caution must be used regarding the use of the following medications during participation in the trial:

- Moderate CYP3A4/CYP2C9 inhibitors and inducers.
- CYP2C8, CYP2B6 and CYP2C19 inhibitors and inducers.

Details of all medications, therapies and supplements administered within 93 days prior to the Visit 1 (Screening visit) until the end of the study will be recorded in the eCRF. Prior medications are defined as those medications that stop prior to administration of first treatment at Visit 2; concomitant medications are defined as those medications started after first administration of study drug at Visit 2 until the end of study.

5.8 Conventional Attack Treatment

Conventional attack treatment is permitted after 4h, or earlier as warranted, following study drug intake, provided HAE attack symptoms are judged severe enough by the subject to require treatment as per the subject's usual treatment regimen, or are deemed ineligible for study drug treatment, or are associated with laryngeal or facial symptoms. Subjects are permitted to treat their HAE attacks with their conventional attack treatment (pdC1INH or rhC1INH iv or icatibant).

Subjects will attempt to contact their study physician or qualified designee prior to use of conventional attack treatment. The dedicated study physician or qualified designee should confirm that conventional attack treatment is appropriate per the protocol and HAE attack severity. Should the subject be unable to reach their study physician or qualified designee prior to taking conventional attack treatment, subjects may take their conventional attack treatment as needed. Time to use of conventional attack treatment will be entered in the subject diary.

Note: In the event a subject receives treatment with C1INH or icatibant (all doses) during the study, the following washout periods are required prior to the subsequent dosing with the study drug:

- 7-day washout period required for C1INH.
- 3-day washout period required for icatibant.

6 VARIABLES AND METHODS OF ASSESSMENT

6.1 Efficacy Variables

Efficacy variables of interest in this study are:

- Time to use of conventional attack treatment captured in the subject diary.
    - What time did you take your conventional HAE attack medication?
- Overall HAE attack severity assessed on the PGI-S (5LS) scored as none, mild, moderate, severe and very severe.
    - Please indicate the overall severity of your HAE attack right now.
- Change in HAE attack severity assessed using the PGI-C (7TQ), scored as Much better / Better / A little better / No change / A little worse / Worse / Much worse.
    - How would you describe your overall HAE attack symptoms right now, compared to how you were when you took the study drug?
- The type of HAE attack symptoms (abdominal pain, skin pain and skin swelling) each assessed on a 100 mm visual analogue scale (VAS) anchored at 0 (none) and 100 (very severe).
    - How much abdominal pain / skin pain / skin swelling are you experiencing right now?

6.2 Safety Variables

Safety variables of interest in this study are:

- AEs, including SAEs.
- Laboratory test results (clinical chemistry, hematology, coagulation, and urinalysis)
- Vital signs (SBP, DBP, PR, RR and body temperature).
- Physical examination findings.
- ECG results.

6.2.1 Adverse Events

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. It is the Investigator's responsibility to ensure compliance with reporting of AEs from his/her site.

An AE is defined as any untoward medical occurrence associated with the use of an IMP in humans, whether or not considered IMP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, without any judgment about causality. An AE can arise from any use of the IMP (e.g. off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose.

All AEs spontaneously reported by the subject and / or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF.

Any clinically relevant deterioration in a clinical finding is considered an AE and must be recorded.

Laboratory abnormalities or other abnormal assessments (e.g., physical examination, vital signs, etc.) that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) should be reported as AEs (unless they are associated with an already reported clinical event).

6.2.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him / her by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

6.2.1.2 Relationship to Study Drug

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE.

Types of evidence that would suggest a causal relationship between the study drug and the AE include: A single occurrence of an event that is uncommon and known to be strongly associated with study drug exposure (e.g. hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with study drug exposure, but is otherwise uncommon in the population exposed to the study drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the study drug-sequence group than in a concurrent or historical control group.

6.2.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected*: An AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.
- *Expected*: An AE that is listed in the IB at the specificity and severity that has been observed.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological / mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an AE, but the final classification is subject to the Sponsor's determination.

6.2.1.4 Serious Adverse Events

An AE is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.

  Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24h). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute / intensive care inpatient unit. Inpatient hospitalization does not include: Emergency room visits; outpatient / same-day / ambulatory procedures; observation / short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research / phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly / birth defect.
- Important medical events.

  Note: Important medical events may not result in death, are life-threatening, or require hospitalization and may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.2.1.5 Reporting Adverse Events

All AEs which occur from the time of signing of the ICF up to and including Visit 4 / Early Discontinuation, must be recorded in the eCRF.

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to the study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

If an AE increases in severity it will be recorded as a new AE.

6.2.1.6 Reporting Suspected Unexpected Adverse Reactions

A SUSAR is an AE that meets all the following criteria:

- Serious
- Unexpected
- Reasonable possibility of a causal relationship between the AE and the study drug.

SUSARs are to be reported to Orion Pharmacovigilance (PV) within 24h of awareness. All SUSARs should be reported to the relevant Regulatory Authority, Independent Ethics Committee (IEC), Institutional Review Board (IRB) and investigators as per the regulatory requirement and timelines.

6.2.1.7 Reporting Serious Adverse Events

All SAEs, regardless of relationship to the study drug, must be immediately reported on the SAE form within 24h of awareness by any site staff. If it is not possible to complete all sections of the SAE form within 24h of becoming aware of the SAE, transmission of the form must not be delayed and the outstanding information should be sent on a follow-up SAE form. All information relevant to the SAE must be recorded on the appropriate eCRF. The Investigator is obligated to pursue and obtain information requested by Orion PV and / or the Sponsor in addition to that information reported on the SAE form and eCRF. All subjects experiencing a SAE must be followed up and the outcome reported.

The Investigator should obtain and maintain in his / her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Orion PV and the Sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug.

Contact information for Orion PV (SAEs):

[redacted]

6.2.1.8 Reporting Adverse Events to Independent Ethics Committees / Regulatory Authorities

The Investigator is responsible for informing the local IEC/ central IRB of the applicable safety reports in compliance with local regulations. Copies of all correspondence and documentation relating to reporting of any safety reports to the local IEC/ central IRB should be maintained in the Investigator Site Files.

The Sponsor, or its designee, Orion Clinical Services, will inform Investigators, central IECs and regulatory authorities of applicable safety reports, as required.

6.2.1.9 Adverse Event Follow-up

All AEs irrespective of the suspected causality, will be monitored until the AE has resolved or until the end of the study, unless the subject is lost to follow–up or withdraws consent or the subject died prior to the end of the study. All SAEs, irrespective of the suspected causality, will be monitored until the SAE has resolved or until the subject is lost to follow-up or the subject has died.

6.2.1.10 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the Investigator to Orion PV on the pregnancy notification form immediately after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to Orion PV on the pregnancy outcome form immediately after becoming aware of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24h in accordance with the procedure for reporting SAEs.

If a female partner of a male study subject who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored according to the same guidelines as for female subjects who become pregnant during the study.

6.2.2 Laboratory Variables

Laboratory assessments as detailed in Table 1 will be performed by a laboratory. Before starting the study, the lab will supply a list of the normal ranges and units of measurement.

Blood samples (approximately 50 mL) will be taken using standard venipuncture techniques. A lab manual will be provided by the laboratory; this will contain very detailed instructions for collection, storage, and shipment of samples (e.g., what kind of tubes, what kind of sample preparation, mailing addresses, etc.).

The laboratory variables as detailed in Table 1 will be determined in accordance with the Schedule of Procedures (Table 3).

Table 1: Laboratory Assessments

Hematology:	erythrocytes MCV MCH Neutrophils Eosinophils Basophils Lymphocytes Monocytes Platelets Leukocytes Hemoglobin Hematocrit	Urinalysis:	pH Protein Glucose Ketone Bilirubin Blood Nitrite Microalbuminemia Proteinuria
Clinical chemistry:	HgA1c Creatinine Glucose Triglycerides Urea Uric acid Bilirubin Cholesterol	Liver enzymes:	Alkaline phosphatase AST ALT GGT
Electrolytes:	Sodium Potassium	Coagulation:	PT, aPTT
Pregnancy test:	In female subjects of childbearing potential. Serum pregnancy test at all visits; urine pregnancy test at Visit 2 as well to confirm pregnancy status prior to dosing.		
Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; HgA1c = Glycosylated hemoglobin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; pH = potential hydrogen; PT = prothrombin time.			

The Investigator must review screening laboratory results for subject eligibility prior to enrolling.

Laboratory tests can be repeated at the Investigator's discretion and any associated safety issue should be followed up as per the Investigator's clinical judgement until resolution / stabilization.

Laboratory data will be electronically transferred to the clinical database at specified time points during the study.

6.3 Methods of Assessment

The following assessments will be conducted and recorded in the eCRF. The Schedule of Procedures and Procedures by Visit can be found in Sections 7.1 and 7.2, respectively.

6.3.1 Subject Demography

Subject demography will be performed at Visit 1 (Screening visit) and consists of:

- Date of birth
- Height (meters [m]; without shoes)
- Weight (kilograms [kg]; without shoes or overcoat)
- Race and ethnicity
- Gender

6.3.2 Medical History

For the documentation of the medical history, any relevant previous and concurrent diseases will be documented.

The medical history will be obtained by interviewing the subject or by inspecting relevant medical records.

For coding of medical history, see Section 9.4.

6.3.2.1 HAE Disease History

HAE disease history will be recorded at Visit 1 (Screening visit). For disease history the following will be documented:

- Date of first symptoms of HAE
- Date of first diagnosis of HAE
- HAE attack profile in the past 93 days
    - Location of the attacks
    - Number of the attacks
    - Maximum severity of the attacks
- Family history of HAE
- Most recent C1-INH antigen or functional level as per medical history
- Most recent C4 level as per medical history

6.3.3 Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.7.

6.3.4 Vital Signs

Vital signs will be assessed at rest (5 minutes in a supine position) in accordance with the Schedule of Procedures (Table 3). Vital signs should be conducted prior to study drug administration and 1h and 4h post-study drug administration during Part 1.

Vital signs include:

- Blood pressure (SBP and DBP; mmHg)
- PR (beats per minute)
- Respiration rate (breaths per minute)
- Body temperature (°C)

6.3.5 Physical Examinations

Complete physical examinations will be performed in accordance with the Schedule of Procedures (Table 3).

6.3.6 Electrocardiogram

A 12-lead ECG recorded over at least 10 seconds after the subject has rested supine on a bed for at least 5 min. HR, PR, QRS, QT and RR will be recorded; QTcF calculated as per standard practice.

6.3.7 Safety Laboratory Assessments

Laboratory assessments will be conducted in accordance with Section 6.2.2. The laboratory will provide a lab manual with detailed procedures. Safety labs will be collected per the Schedule of Procedures (Table 3).

6.3.8 Efficacy Assessments

Efficacy assessments will be performed in accordance with the Schedule of Procedures (Table 3).

There are no efficacy assessments in Part 1.

In Part 2, following study drug intake, subject assessments of overall HAE attack severity and change in HAE attack severity will be undertaken as follows (Table 2):

Table 2: Frequency of Subject Assessment

Time Period following Study Drug Administration	Frequency of Subject Assessment*	Allowed Time Window for Assessment
0h – 4h	Every 30 min	None
4h – 12h	Every 1h	+/- 15 min
12h – 24h	Every 3h	+/- 30 min
36h	Once	+/- 60 min
48h	Once	+/- 60 min

*In the event that **conventional attack treatment is used** (Section 5.8), the subject should perform assessments every 30 min for 4h following first administration of conventional attack treatment. After this, the subject should revert back to original frequency of assessments based on time of study drug administration.

6.3.9 Pharmacokinetic Blood Sampling

Not applicable for US study sites.

6.3.10 Pharmacodynamic Assessments

Not applicable for US study sites.

7 STUDY CONDUCT

7.1 Schedule of Procedures

A list of procedures to be conducted, by visit, is described in Table 3.

Table 3: Schedule of Procedures

	Screening	Part 1	Part 2			End of Study/ED*
Clinic Visit (V)	**Visit 1**	**Visit 2***	**1st eligible# HAE attack**	**Visit 3***	**2nd eligible# HAE attack**	**Visit 4***
Informed Consent	X					
Eligibility Assessment	X	X				
Medical History[a]	X					
Demographics[b]	X					
Physical Examination[c]	X	(X)[c]		X		X
Vital Signs[d]	X	X[a]		X		X
Electrocardiogram[m]	X	X[m]		X		X
Safety Laboratory[e]	X	X[e]		X		X
Pregnancy Test[f]	X serum	X[f] serum & urine		X serum		X serum
Concomitant Medications	X	X		X		X
Adverse Events[g]	X	X		X		X
Randomize subject		X				
Subject Diary completion training, dispensing and return		X		X		X[i]
C1INH / icatibant washout check[j]		X	X		X	
Dose[k]		X	X		X	
Study drug dispensing and return		X		X		X[i]
Overall attack severity (PGI-S 5LS)[h]			X		X	
Change in attack severity (PGI-C 7TQ)[h]			X		X	
Abdominal pain (VAS)[h]			X		X	
Skin pain (VAS)[h]			X		X	
Skin swelling (VAS)[h]			X		X	
24h telephone follow-up[l]			X		X	

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ED = early discontinuation; HAE = hereditary angioedema; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; 5LS=5-point Likert scale; 7TQ=7-point transition question; VAS=visual analogue scale;

*Visit 2 to occur within 28 days of Visit 1 (Screening visit).

*Visit 3 to occur as soon as is practicable (within 7 days) following the 1st home-treated HAE attack.

*Visit 4 to occur as soon as is practicable (within 7 days) following the 2nd home-treated HAE attack. Upon subject withdrawal, Visit 4 to be completed as soon as possible and, whenever possible, prior to starting any new medication or treatment.

When a HAE attack occurs, the subject will telephone the dedicated study physician or qualified designee with a description of the HAE attack documented in the Subject Diary. The dedicated study physician or qualified designee will confirm if the HAE attack is eligible for treatment with the study drug (Section 7.2.2.2). If the HAE attack is not eligible for treatment with the study drug, the subject will commence conventional attack treatment.

[a] Medical history includes any relevant previous and concurrent diseases, HAE disease history (date of first symptoms of HAE; date of first diagnosis of HAE; HAE attack profile in the past 93 days [location of the attacks; number of the attacks; maximum severity of the attacks]; family history of HAE; most recent C1-INH antigen or functional level as per medical history; most recent C4 level as per medical history) and therapies and supplements taken within the past 93 days, previous participation in interventional clinical studies in the past 93 days.

[b] Demographics: Date of birth; height (meters [m]; without shoes); weight (kilograms [kg]; without shoes or overcoat); race and ethnicity; gender. Calculation of BMI will be automated in the database.

[c] Complete physical examination. Physical examination at Visit 2 if clinically indicated.

[d] Vital signs include pulse rate (PR), respiratory rate (RR), systolic and diastolic blood pressure (SBP, DBP), and body temperature (°C). Visit 2: Vital signs taken pre-dose (0h), 1h, and 4h post-dose.

[e] Laboratory assessments performed by a laboratory as described in Table 1. Visit 2 labs collected at 4h post-dose.

[f] Female subjects of childbearing potential.

- Visit 1: Serum pregnancy test;
- Visit 2: Serum and urine pregnancy test; collected prior to study drug dosing;
- Visit 3: Serum pregnancy test;
- Visit 4: Serum pregnancy test.

[g] AEs recorded from the time of signing of the informed consent form (ICF) up to and including to Visit 4 / ED.

[h] The subject complete timed assessments of his / her HAE attack symptoms for a 48h period following drug intake as documented in Table 2.

[i] Study drug and Subject Diary return only.

[j] Note: In the event a subject receives treatment with C1INH or icatibant (all doses) during the study, the following washout periods are required prior to the subsequent dosing with study drug:

- 7-day washout period required for C1INH.
- 3-day washout period required for icatibant.

[k] Note: A minimum of 48-hour washout period required between each dose of study drug.

[l] The dedicated study physician or qualified designee will contact the subject within 24h of the eligible HAE attack to confirm the subject's safety and wellbeing.

[m] A 12-lead ECG recorded over at least 10 seconds after the subject has rested supine on a bed for at least 5 min. HR, PR, QRS, QT and RR will be recorded; QTcF calculated as per standard practice.

- Visit 2: ECG performed within 30 min pre-dose and approximately 1h post-dose.

7.2 Procedures by Visit

Prior to any study activities, subjects will be asked to read and sign an ICF that has been approved by an IEC/ IRB and the Sponsor and which complies with regulatory requirements.

All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

7.2.1 Screening Phase

7.2.1.1 Visit 1

Subjects will undergo screening during Visit 1. Following full discussion of the study and the signing of the ICF, a screening subject ID number will be assigned (Section 4.5).

The following screening and baseline assessments will be performed:

- Eligibility assessment evaluating all results of the screening assessment results against the inclusion and exclusion criteria (Section 4).
- Full medical history (Section 6.3.2), including HAE history (Section 6.3.2.1), concomitant illnesses / diseases and medications (Section 6.3.3), therapies and supplements taken within the past 93 days, previous participation in interventional clinical studies in the past 93 days.
- Demographic information including race, ethnicity and date of birth (Section 6.3.1).
- Height (m; without shoes) and weight (kg; without shoes or overcoat) (Section 6.3.1). Calculation of body mass index (BMI) will be calculated automatically in the database.
- Complete physical examination (Section 6.3.5).
- Vital signs (SBP and DBP, PR, RR, and body temperature). BP and PR recorded after subject has been supine for 5 minutes (Section 6.3.4).
- 12-lead ECG (Section 6.3.6).
- Blood and urine samples (Section 6.3.7).
- Serum pregnancy test (female subjects of childbearing potential).
- AEs recorded from time of ICF signature (Section 6.2.1).
- Review the study procedures and study visit schedule with the subject.

7.2.2 Treatment Phase

7.2.2.1 Part 1: Visit 2

Subjects should attend the clinic for Visit 2 within 28 days following Visit 1 (Screening visit).

The following assessments will be performed:

- Reconfirm eligibility (Section 4).
- Physical examination (if clinically indicated) (Section 6.3.5).
- Vital signs (SBP and DBP, PR, RR, and body temperature): Pre-dose (0h), 1h, and 4h post-dose (Section 6.3.4).
- 12-lead ECG (within 30 min pre-dose and approximately 1h post-dose) (Section 6.3.6).
- Blood and urine samples collected 4h post-dose (Section 6.3.7).

- Serum and urine pregnancy test (female subjects of childbearing potential); collected prior to study drug dosing.
- Change to the concomitant medication (Section 6.3.3).
- Review and collection of AEs (Section 6.2.1).
- Randomize subject.
- Dispense Subject Diary and provide Subject Diary completion training.
- Check washout periods for treatment with C1INH or icatibant (all doses) have been respected prior to dosing with the study drug:
    - 7-day washout period required for C1INH.
    - 3-day washout period required for icatibant.
- Administer the study drug (KVD900 600 mg [equivalent to 6 x 100 mg tablets]) (Section 5.2).
- Dispense study drug to be taken at first HAE attack.

Following a check on the subject's well-being and safety, and a recap of the procedures to be followed in relation to HAE attacks at home, the subject may be discharged from the clinic once the 4h post-dose procedures have been completed.

7.2.2.2 Part 2: First HAE attack

When an attack of HAE occurs, the subject will telephone the dedicated study physician or qualified designee with a description of the HAE attack documented in the Subject Diary. This description will include:

- Attack location.
- Attack symptoms (e.g. swelling, pain, vomiting).
- Time of onset.
- Attack severity.
- Time of last substantial meal.

The dedicated study physician or qualified designee will assess the HAE attack against the following criteria for a qualifying attack:

- Attack location below the neck (laryngeal or facial attacks are not eligible).
- Attack onset < 1h.
- Attack severity less than severe on the PGI-S (5LS).

The dedicated study physician or qualified designee will check that the following washout periods for treatment with C1INH or icatibant (all doses) have been respected prior to dosing with the study drug:

- 7-day washout period required for C1INH.
- 3-day washout period required for icatibant.

If all these criteria are met, the dedicated study physician or qualified designee will instruct the subject to take the assigned study drug for the first eligible HAE attack. This will consist of

6 tablets, each containing either 100 mg KVD900 (total dose 600 mg) or matching placebo tablets. If the HAE attack is not eligible for treatment with the study drug, the subject will commence conventional attack treatment.

The subject will then complete timed assessments of his / her HAE attack symptoms for a 48h period following drug intake as documented in Table 2.

Overall HAE attack severity will be assessed on the PGI-S (5LS) scored as none, mild, moderate, severe and very severe.

Change in HAE attack severity will be assessed using the PGI-C (7TQ), scored as Much better / Better / A little better / No change / A little worse / Worse / Much worse.

The type of HAE attack symptoms (abdominal pain, skin pain and skin swelling) will each be assessed on a 100 mm VAS anchored at 0 (none) and 100 (very severe).

Conventional attack treatment is permitted after 4h, or earlier as warranted, following study drug intake, provided HAE attack symptoms are judged severe enough by the subject to require treatment as per the subject's usual treatment regimen, or are deemed ineligible for study drug treatment, or are associated with laryngeal or facial symptoms. Prior to use of conventional attack treatment, subjects will notify the dedicated study physician or qualified designee who will confirm conventional treatment is appropriate per protocol and subject report of symptom severity. Subjects are permitted to treat their HAE attacks with their conventional attack treatment (pdC1INH or rhC1INH iv or icatibant).

The dedicated study physician or qualified designee will contact the subject within 24h of the eligible HAE attack to confirm the subject's safety and wellbeing. Subjects will be instructed to contact the dedicated study physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects are to contact the dedicated study physician or qualified designee or contact the nearest emergency service. The dedicated study physician or qualified designee will be available 24h/day and 7 days/week to receive subject calls.

The dedicated study physician or qualified designee will document all contact with the subject in the subjects' source documentation (i.e., medical records).

7.2.2.3 Part 2: Visit 3

As soon as is practicable (within 7 days), following the first home-treated HAE attack of Part 2, the subject will return to the clinic at which the following procedures will be conducted:

- Collect the Subject Diary containing the subject's assessments relating to the first HAE attack treated in Part 2.
- Accountability of any unused study drug/study drug packaging returned by the subject.
- Vital signs (SBP and DBP, PR, RR, and body temperature; Section 6.3.4).
- 12-lead ECG (Section 6.3.6).
- Complete physical examination (Section 6.3.5).
- Blood and urine samples (Section 6.3.7).
- Serum pregnancy test (female subjects of childbearing potential).
- Changes to concomitant medication (Section 6.3.3).
- Review and collection of AEs (Section 6.2.1).

- Dispense Subject Diary for second HAE attack of Part 2 and provide Subject Diary completion training.
- Dispense assigned study drug to be taken at second HAE attack.

7.2.2.4 Part 2: Second HAE attack

The procedures to be followed by the subject in relation to the second HAE attack during Part 2 will be identical to those described in Section 7.2.2.2 above except that, when so instructed by the dedicated study physician or qualified designee, the subject will take the assigned study drug for the second HAE attack.

Note: A minimum of 48-hour washout period required between each dose of study drug.

7.2.3 End of Study / Early Discontinuation

7.2.3.1 Visit 4

As soon as is practicable (within 7 days) following the second home-treated HAE attack of Part 2, the subject will return to the clinic within 7 days for Visit 4 at which the following procedures will be conducted:

- Collect the Subject Diary containing the subject's assessments relating to the first and second treated HAE attacks in Part 2.
- Accountability of any unused study drug / study drug packaging returned by the subject.
- Vital signs (SBP and DBP, PR, RR, and body temperature; Section 6.3.4).
- 12-lead ECG (Section 6.3.6).
- Complete physical examination (Section 6.3.5).
- Blood and urine samples (Section 6.3.7).
- Serum pregnancy test (female subjects of childbearing potential).
- Change to the concomitant medication (Section 6.3.3).
- Change in AE status (Section 6.2.1).

Following completion of study procedures and dosing, subjects will resume their standard treatment and medical care for HAE.

7.2.4 Early Discontinuation / Withdrawal

If any subject discontinues the trial early *(*Section 4.3*)*, every effort should be made to complete Visit 4 (Section 7.2.3*)* as soon as possible and, whenever possible, prior to starting any new medication or treatment. All attempts will be made to avoid early discontinuation.

Once approximately 50 subjects have successfully completed Parts 1 and 2 of the study, the remaining enrolled subjects will be asked to return to the clinic for Visit 4 and return all unused study drug (Section 7.2.3).

8 STATISTICAL METHODS

The statistical considerations in this section summarize the plan for data analysis of this study. Before unblinding, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below. The SAP will supersede the protocol in the case of any inconsistencies between the two documents. Any deviations from the planned analyses described in the SAP will be described and justified in the final Clinical Study Report.

Subjects will be randomized in a 1:1 ratio to 1 of the 2 sequence groups for Part 2: KVD900 600 mg followed by placebo or placebo followed by KVD900 600 mg.

8.1 Study Subjects

8.1.1 Disposition of Subjects

The number and percentage of subjects screened, entering and completing each study part will be presented, stratified by treatment. Reasons for withdrawal pre- and post-randomization will also be summarized.

8.1.2 Protocol Deviations

Deviations from the protocol including violations of inclusion / exclusion criteria will be assessed as “minor” or “major” in cooperation with the Sponsor. Major deviations from the protocol that have the potential to impact the efficacy results will lead to the exclusion of a subject from the Per Protocol Set (PPS). Deviations will be defined prior to unblinding.

8.1.3 Analysis Sets

Analysis sets are defined as follows:

- Safety set (SAF): Subjects who have taken at least one dose of study drug (including the study drug dose in Part 1).
- Full analysis set (for efficacy) (FAS): All randomized subjects who received both doses of study drug in Part 2.
- Per protocol set (for efficacy) (PPS): Randomized subjects in Part 2 who received both doses of study drug in Part 2 and have no major protocol deviations.
- PK / PD analysis set: All subjects for whom PK / PD samples were taken in Part 1. (Note: Subjects enrolled at US study sites will not contribute data for PK and PD analysis.)

The primary efficacy analysis will be based on the FAS. A secondary analysis will also be performed based upon the PPS unless the FAS and PPS are the same. All safety analyses will be based upon the SAF.

Demographic and baseline characteristics will be evaluated for the SAF, FAS and for the PPS. If one or more subject(s) received incorrect trial drug, these data will also be presented for the SAF.

8.2 General Considerations

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated. Continuous data will be summarized by treatment group using descriptive statistics (number, arithmetic mean, median, standard deviation [SD], minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages).

All analyses will be carried out using SAS Version 9.4 or higher or using other validated software.

Analysis and data conventions:

Definition of baseline

The baseline assessment will be the latest, valid pre-dose assessment available for each dose in Part 1 and Part 2.

Unscheduled assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

Missing data conventions

Statistical handling of missing assessments, e.g. measurements not collected during sleep at night, will be outlined in the SAP.

Multiplicity Considerations

No multiplicity adjustments are planned in this Phase 2 study.

Other considerations

Treatment by centre interactions will not be conducted. Any outliers that are detected during the blinded review of the data will be investigated. If necessary, queries will be issued to the Investigator, to either correct or confirm the outlier.

8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, concomitant diseases, and concomitant medications will be summarized via descriptive statistics, as appropriate, (overall and by sequence group).

Medical history, concomitant medications and AEs will be coded to Medical Dictionary for Regulatory Activities (MedDRA Version 21.0 or higher) and World Health Organization (WHO) Drug dictionaries, as appropriate, for the purpose of summarization.

8.4 Treatment Compliance

Study drug in Part 1 of the study will be administered under the direct supervision of the site staff and hence compliance is not expected to be problematic.

Compliance in Part 2 of the study will be assessed by review of returned study drug and subject diaries. Non-compliance is not expected to be significant, given the single treatment and short length of the assessment period.

Refer also to Section 5.6.

8.5 Efficacy Analyses

All efficacy variables will be displayed in subject listings.

8.5.1 Primary Efficacy Analysis

8.5.1.1 Hypothesis to be Tested

The null hypothesis is that the time to use of conventional attack treatment following KVD900 treatment and the time to conventional attack treatment following placebo treatment are identical:

H0: $t_k - t_p = 0$,

where t_k is the time to use of conventional attack treatment following KVD900 treatment in Part 2 and t_p is the time to conventional attack treatment following placebo treatment.

The alternative hypothesis is that the time to use of conventional attack treatment following KVD900 treatment is different from the time to conventional attack treatment following placebo treatment:

Ha: $t_k - t_p \neq 0$.

8.5.1.2 Statistical Methods

The primary endpoint, time to use of conventional attack treatment within 12h of study drug, will be analyzed using a [redacted] to reflect the repeat measures on each subject. Subjects will be treated as censored if conventional attack treatment is not used within 12h of study drug.

8.5.2 Secondary and Exploratory Efficacy Analyses

The secondary efficacy endpoints, which will be analyzed for Part 2 of the study, are:

- PGI-S (5LS):
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use conventional attack treatment within 12h of study drug.
    - Time to (1) worsening by one level or more from baseline, or (2) use of conventional attack treatment, whichever comes first within 12h of study drug.

- PGI-C (7TQ):
  - Improvement:
    - Time to symptom relief (*A little better* or higher, 2 time points in a row) within 12h of study drug.
- Visual Analogue Scale (VAS):
  - Improvement:
    - Time to symptom relief (50% reduction from baseline in composite VAS, 3 time points in a row) within 12h of study drug.

The exploratory endpoints are:

- Use of Conventional Treatment:
  - Proportion of HAE attacks that require conventional attack treatment within 12h and 24h of study drug.
  - Time to use of conventional attack treatment within 24h of study drug.
- PGI-S (5LS):
  - AUC:
    - Cumulative PGI-S (5LS) expressed as AUC within 12h and 24h of study drug.
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 24h of study drug.
    - Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 24h of study drug.
  - Worsening Only:
    - Time to worsening by one level or more from baseline within 12h and 24h of study drug.
  - Improvement:
    - Proportion of HAE attacks that improve by one level or more from baseline within 12h and 24h of study drug.
    - Time to improvement by one level or more from baseline within 12h and 24h of study drug.
    - Proportion of subjects with HAE attack resolution (rating of *none*) within 12h and 24h of study drug.
    - Time to HAE attack resolution (rating of *none*) within 12h and 24h of study drug.
  - Stable or Improvement:
    - Proportion of HAE attacks that are stable or improved from baseline within 12h and 24h of study drug.
- PGI-C (7TQ):
  - AUC:
    - Cumulative PGI-C (7TQ) expressed as AUC within 12h and 24h of study drug.
  - Worsening (including use of conventional attack treatment):

        - Proportion of HAE attacks that are (1) rated *A little worse* or higher, 2 time points in a row or (2) use of conventional attack treatment within 12h and 24h of study drug.
        - Time to HAE attack being (1) rated *A little worse* or higher, 2 time points in a row, or (2) use of conventional attack treatment, whichever comes first, within 12h and 24h of study drug.
    - Worsening Only:
        - Time to HAE attack being rated *A little worse* or higher, 2 time points in a row, within 12h and 24h of study drug.
    - Improvement:
        - Proportion of HAE attacks that are rated *A little better* or higher, 2 time points in a row, within 12h and 24h of study drug.
        - Time to HAE attack being rated *A little better* or higher, 2 time points in a row, within 24h of study drug.
        - Proportion of HAE attacks that are rated *Better* or higher within 12h and 24h of study drug.
        - Time to HAE attack being rated *Better* or higher within 12h and 24h of study drug.
    - Stable or Improvement:
        - Proportion of HAE attacks that are stable or improved within 12h and 24h of study drug.
- Visual Analogue Scale (VAS):
    - AUC:
        - Cumulative composite VAS expressed as AUC within 12h and 24h of study drug.
    - Improvement:
        - Proportion of HAE attacks with symptom relief (50% reduction from baseline in composite VAS, 3 time points in a row) within 12h and 24h of study drug.
        - Time to symptom relief (50% reduction in composite VAS, 3 time points in a row) within 24h of study drug.

For comparisons of proportions, [redacted] will be used to compare the treatment arms. Secondary and exploratory endpoints, using *time to event* as the unit of analysis, will be analyzed in the same way as the primary endpoint, [redacted].

8.6 Safety Analyses

Safety endpoints include AEs / SAEs, physical exam findings, ECG results, laboratory test results (clinical chemistry, hematology, coagulation, and urinalysis), and vital signs (SBP, DBP, PR, RR and body temperature).

8.6.1 Adverse Events

AEs will be coded using the MedDRA dictionary (v21.0 or higher). Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs

causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it 1) occurs after the first dose of study drug in Part 1 or Part 2 or 2) if it is present prior to receipt of randomized study treatment but worsens in severity or increases in frequency after the first dose of study drug.

Frequency counts will be given of subjects with TEAEs by system organ class (SOC) and preferred term; by SOC, preferred term and maximal severity; by SOC, preferred term and strongest relationship; by SOC and preferred term for SAEs; and by SOC, preferred term, and day of onset. AEs will be classified by SOC and preferred term in the MedDRA coding dictionary. AEs will be tabulated both as the total events (regardless of relationship to treatment) and as drug-related events (by treatment period: (1) active, combined for treatment taken in Part 1 and Part 2, and (2) placebo (taken in Part 2). The number of subjects with one or more events versus no events will be calculated for each treatment.

Subject listings of all AEs will be provided as well as listings of deaths, SAEs, and AEs leading to discontinuation.

The following summaries will be provided:

- Relationship between AE SOC and verbatim text.
- On-treatment AEs: Number and percentage of subjects reporting each AE, each AE leading to withdrawal, each SAE, each drug-related SAE, each fatal AE, and most frequent by treatment.
- Post-treatment AEs: Number and percentage of subjects reporting each AE.
- Listing of all AEs.
- Summary of Most Frequent AEs.

8.6.2 Laboratory Assessments

Laboratory assay results include clinical chemistry, hematology, coagulation, and urinalysis. Continuous parameters will be summarized using descriptive statistics for each treatment group and for all subjects at each visit. Changes from baseline will also be summarized for each treatment group and for all subjects where appropriate. Each categorical parameter will be summarized using frequency counts and percentages for each treatment group and for all subjects. A shift table of the changes from baseline will also be presented.

The high / low criteria will be determined based on the reference ranges provided by the laboratory. Summaries of assessments outside the normal range and the changes from baseline relative to the normal range will also be produced. A subject listing of laboratory assessments will also be produced and will include changes from baseline at each visit. Data from subjects who have values outside the normal range will be specified in this listing.

8.6.3 Vital Signs

Vital sign measurements, including PR, RR, blood pressure (SBP, DBP), and body temperature will be summarized for baseline (pre-treatment, Visit 2).

PR, RR, blood pressure (SBP, DBP) and body temperature will be summarized by time point throughout Part 1 using continuous descriptive statistics for all subjects. Change from baseline during Part 1will also be summarized for all subjects.

SBP and DBP, PR, respiration rate, and body temperature will be summarized by treatment group at Visit 3 and Visit 4.

A subject listing will also be produced and will include changes from baseline by time point throughout Part 1.

8.6.4 Physical Examination

A subject listing of the Visit 1 (Screening), Visit 3, and Visit 4 physical examination findings will be produced.

8.6.5 Electrocardiograms

Twelve-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values as well as change from baseline at each time point will be summarized descriptively in tabular format. An ECG shift table will be presented. Clinically significant worsening from baseline or new clinically significant ECG abnormalities that were considered AEs by the Investigator will be presented in the AE analyses.

8.7 Pharmacokinetic / Pharmacodynamic Analysis

Note that PK/PD blood samples will not be collected from subjects enrolled at US study sites.

8.7.1 Pharmacokinetic Analysis

Non-compartmental PK parameters will include, but are not limited to, maximum concentration in plasma (C_{max}), time to reach C_{max} in plasma (t_{max}), area under the curve from time 0 to last measurable concentration (AUC_{0-t}), apparent clearance (CL/F), apparent volume of distribution (Vd/F) and estimated terminal elimination half-life (t½). A complete list of PK parameters planned to be calculated will be described in the SAP.

The PK parameters of KVD900 will be determined from the individual concentration versus time data using Phoenix WinNonlin. In case of a deviation from the theoretical time, the actual time of blood sample will be used in the calculation of the derived PK parameters. Individual concentrations and derived PK parameters of KVD900 in plasma will be listed and summarized for each treatment. Individual and geometric mean concentration-time data will be plotted on linear and semi-logarithmic scales.

8.7.2 Pharmacodynamic Analysis

KVD900's effect on PKa activity will be analyzed using two exploratory measures of PKa enzyme activity in plasma:

- [redacted]
- [redacted]

The PD will be summarized for each treatment. Individual and mean data will be provided as a report addendum located in the appendix of the final Clinical Study Report.

8.8 Interim Analyses

No interim analyses are planned.

8.9 Determination of Sample Size

Approximately 60 subjects will be enrolled to ensure that approximately 50 subjects complete the study. A sample size of approximately 50 subjects completing both treatment periods (25 per sequence) is proposed to provide 90% power for testing at the 5% alpha level (2-sided) for the primary endpoint of time to use of conventional attack treatment within 12h of study drug. [redacted] The assumption of minimal correlation should be a conservative assumption with respect to sample size.

An oversampling by 20% (10 subjects) is proposed to account for subjects that may not complete both treatment periods due to infrequent or ineligible HAE attacks or for subjects who discontinue the trial early, for whatever reason. Thus, study enrolment will be considered sufficient to address the primary efficacy hypothesis after approximately 50 subjects have completed both treatment periods. Since further exposure is not required and could be considered unnecessary, ongoing subjects who have not completed both periods will be asked to return to the study site and complete Visit 4 (Early Discontinuation visit). Data from all subjects, complete and incomplete, will be analyzed in the safety set.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. All information recorded on the eCRF system for this study must be consistent with the subjects' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study centre using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data centre, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible Orion CRA or data manager will raise a query in the electronic data collection (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the eCRF page will be frozen.

The specific procedures to be used for data entry and query resolution using the EDC system / eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system / eCRF.

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRF. All source documents from which eCRF entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments, and study specific examinations.

Data that will be entered directly into the eCRF system (i.e., for which there is no prior written or electronic record of data) are considered to be source data.

The original eCRF entries for each subject may be checked against source documents at the study site by the Orion CRA.

After review by the Orion CRA, completed eCRF entries will be uploaded and forwarded to Orion. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system / eCRF.

9.2.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an on-line web-based EDC system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each subject included in the study and should reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data–check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on–line directly by the Investigator or by authorized staff. Off–line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study product dispensed to the subject and any dosage changes will be tracked on the eCRF.

9.3 Access to Source Data

During the study, the Orion CRA will make site visits to review protocol compliance, compare eCRF entries and individual subject's source medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IECs, IRBs and / or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and / or on–site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures Orion and the Sponsor of the necessary support at all times.

9.4 Data Processing

All data will be entered by site personnel into the EDC system / eCRF (as detailed in Section 9.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query / correction sheets for unresolved queries will be sent to the study CRAs for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the WHO Drug Reference List (DRL), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history / current medical conditions and AEs will be coded using the MedDRA terminology.

Previous and concomitant diseases as well as AEs will be coded with MedDRA.

The versions of the coding dictionaries will be provided in the Clinical Study Report.

9.5 Archiving Study Records

According to International Council on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice (GCP)[2] guidelines of the ICH, and of the Declaration of Helsinki (2013)[3]. The study also will be carried out in keeping with local legal requirements.

9.7 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator or designee must explain orally and in writing the nature, duration, and purpose of the trial, and the action of the study drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The subject will be informed that he / she is free to withdraw from the trial at any time. The subject will be given sufficient time to ask questions, understand and to take a decision on his participation. The consent form must be dated and signed by both the subject and the person obtaining the consent in two copies. One of the copies will be given to the subject and the other will be retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC, IRB and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

[2] International Council for Harmonization (ICH) E6 – Good Clinical Practice (GCP) (R2).
[3] World Health Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. (as adopted by the 64th World Medical Assembly General Assembly, Fortaleza, Brazil, October 2013)

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and / or other relevant documents will be approved by the IEC/ IRB/ Regulatory Authorities. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

Substantial protocol amendments must be submitted to the Regulatory Authority(ies) for approval prior to implementation and to the IECs/IRBs for approval as per local regulations.

Administrative changes which are not deemed substantial may be made without the need for IEC / /IRB/ Regulatory Authority approval. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.9 Duration of the Study

For an individual subject, the maximum duration of the study is likely to be approximately 19 weeks (including up 28 days for screening, 1 day for Part 1, expect up to 93 days duration for subject to experience 2 qualified HAE attacks, and approximately 2 weeks between 2nd HAE attack and Visit 4).

9.10 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Failure to enroll subjects at an acceptable rate.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

The termination of the study after approximately 50 completed subjects is not considered premature termination of the study.

9.11 Confidentiality

Personal data of the subject shall be processed in a manner that ensures it has appropriate security. This includes protection against unauthorized or unlawful processing and against accidental loss, destruction or damage and by using appropriate technical or organizational measures. One such measure is by the Investigator ensuring that the subjects' personally identifiable information is replaced through the use of pseudonymization.

On the eCRFs or other documents submitted to the Sponsor and / or delegate, subjects will NOT be identified by their names but by the assigned subject number and their initials to ensure confidentiality of the subject' information and that data minimization principles are maintained.

If subject names are included in error on copies of documents submitted to Sponsor and / or delegate, the names (except for initials) will be erased or securely destroyed and the assigned subject number added to the document.

The Investigator should keep a separate log (Patient Master List) of patient's codes (assigned patient number), names, addresses, telephone numbers and hospital numbers. The bodily material that is sent to the sponsor and / or delegates (including laboratories) assisting with the study research, will only contain the patient's code. Documents not intended for submission to Sponsor and / or delegate (e.g. signed consent forms) should be maintained by the Investigator in strict confidence and not disclosed to any parties outside of this approved agreement. eCRFs should be protected by use of strong encryption.

All study findings and documents will be regarded as confidential. The Investigator and members of his / her research team must not disclose such information without prior written approval from the Sponsor.

9.12 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators, and IECs/ IRBs.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.13 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. Details are provided in a separate document.

9.14 Insurance

In accordance with legal requirements, the Sponsor will take out insurance covering potential damage for all subjects who participate in the clinical trial prior to commencement of the trial. The name of the insurance company as well as the date of the initial insurance certificate will be provided to the IEC and will be mentioned in the subject information sheet.

All participating subjects or their legal representatives will be informed about the existence of the insurance policy and will have the right to review its terms and conditions.

10 DEFINITION OF END OF TRIAL

The end of trial is defined as last subject last visit.

11 REFERENCE LIST