PROTOCOL TITLE

A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II

Protocol Number:	KVD900-301
Protocol Name:	KONFIDENT
Compound:	KVD900 (300 mg Film-Coated Tablet)
Trial Phase:	3
Sponsor:	KalVista Pharmaceuticals Ltd Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom
IND Number:	143807
EudraCT Number:	2021-001226-21
Date of Protocol:	04 May 2023 (US Only), Version 4.1 11 October 2022 (US Only), Version 3.1 26 May 2022, Version 3.0 10 February 2022, Version 2.0 18 October 2021, Version 1.0
Compliance	This trial will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

1. SIGNATURE PAGE

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II

This trial 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 (World Medical Association 2013) and the guidelines on Good Clinical Practice (GCP).

[redacted]

Chief Medical Officer
KalVista Pharmaceuticals Ltd

[redacted]

Vice President, Clinical
KalVista Pharmaceuticals Ltd

2. DECLARATION OF THE INVESTIGATOR

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II

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

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

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol and will conduct the trial in compliance with regulatory requirements and Good Clinical Practice (GCP).

_____ _____

Investigator Signature Date

_____

Name (block letters)

PROTOCOL AMENDMENT SUMMARY OF CHANGES

The purpose of this amendment is to make statistical analysis changes to the protocol as requested by the US Food and Drug Administration (FDA) and to clarify statistical analyses to be performed for this trial. The changes from Version 3.1 to Version 4.1 of the protocol are as follows:

- Corrected inclusion criterion 6a) to specify that patients who have had at least 2 documented attacks prior to screening meet this inclusion criterion (in addition to patients who have had at least 2 documented attacks prior to randomization).
    - Rationale: The purpose of this change was to correct the inclusion criterion to meet the Sponsor's original intent, which was to ensure that patients are attacking frequently enough to have 3 HAE attacks during the trial period. The 2 documented attacks can occur prior to screening or prior to randomization; however, the protocol inadvertently did not include 'screening' in the criterion.
- Modified the censoring strategy for conventional on-demand treatment from a hypothetical strategy to a composite strategy.
    - Rationale: Per FDA recommendation, receiving conventional on-demand attack treatment should be considered as a treatment failure. Using a composite strategy, time-to-event results for attacks with conventional on-demand attack treatment use will be censored at the end of analysis window, which represents the worst-case scenario.
- Changed the Full Analysis Set definition from requiring IMP treatment for at least 2 periods to just 1 period.
    - Rationale: The analysis method used for the primary analyses doesn't require observations from at least 2 periods. Therefore, this update to the FAS allows more on-treatment attacks to be included in the primary efficacy analyses.
- Added alpha loop-back feature in the multiplicity adjustment strategy.
    - Rationale: The Bonferroni multiplicity adjustment method is conservative; allowing alpha loop-back will improve the power of the hypothesis testing and maintain the overall Type I error rate of 0.05.
- Updated key secondary endpoint #1 to assess sustained improvement by requiring at least 2 time points in a row with the same (or better) measurement.
    - Rationale: This change was made per FDA recommendation. Requiring sustained improvement will reduce the impact of spontaneous or unsustained improvement.
- Added additional subgroup analyses.
    - Rationale: Added subgroup analyses to investigate consistency in treatment effects in additional subgroups.
- Clarified that additional endpoints may be added to the Statistical Analysis Plan.

Minor typographical corrections and editorial changes are not described above.

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3. SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II
Trial No	KVD900-301
Protocol Name	KONFIDENT
Phase	3
Trial Centers	Hereditary angioedema (HAE) treatment centers worldwide
Objectives	**Primary Objective** • To demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks. **Secondary Objective** • To investigate the safety and tolerability of KVD900.
Trial Design & Procedures	KONFIDENT is a double-blind, randomized, placebo-controlled, multicenter clinical trial in patients 12 years or older with HAE type I or II. Patients will be randomized to 6 treatment sequences in a 3-way crossover design. Eligible attacks will initially be treated with a single dose of placebo, 300 mg, or 600 mg KVD900 per attack. If needed (as determined by the patient), a second dose of IMP may be administered for each attack. The estimated duration of this trial for each randomized patient will be approximately 25 weeks from Screening through the Final Visit and includes the treatment of 3 eligible attacks during the Treatment Period. The trial will be conducted at HAE treatment centers worldwide on an outpatient basis and will comprise in-clinic and televisits. A televisit can be conducted via a telephone call or via an interactive audio/video system. **Screening Visit** Eligible patients ≥12 years old will undergo a screening assessment for trial inclusion. All patients will provide informed consent or assent prior to any trial- related procedures being performed. Informed consent and assent may be collected through e-consent if allowed through country and site regulations. During the visit, a physical exam, 12-lead electrocardiogram (ECG), laboratory tests (including diagnostic testing for HAE), and other assessments as outlined in the Schedule of Events (Table 1) will be performed. Site personnel will train patients on the information they will be expected to provide in the electronic diary (eDiary) and the use of investigational medicinal product (IMP). **Randomization Visit** Within 4 weeks of the Screening Visit, patients will participate in a Randomization Visit. Patients will be assigned to receive 3 treatments in randomized, double-dummy

	blinded, crossover fashion based on their assignment to 1 of 6 treatment sequences. Randomization will occur in a 1:1:1:1:1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment sequence. Each patient will receive the following treatments: • 300 mg KVD900 (1 x 300 mg tablet plus 1 matching placebo tablet) • 600 mg KVD900 (2 x 300 mg tablets) • 2 matching placebo tablets Patients will treat each eligible attack with up to 2 doses of IMP, administered at least 3 hours apart. The second dose, if taken, will be the same assigned treatment as the first dose. In this trial, the IMP will be shipped directly to the patients via a courier service or will be dispensed at the trial clinic as required by local regulations or per the site's local practice, as described in the Pharmacy Manual. **Treatment of Eligible HAE Attacks** Patients will treat 3 separate, eligible HAE attacks with their assigned IMP treatment for that attack. For an HAE attack to be considered eligible for treatment with IMP, the attack must meet the following criteria: • The attack is not a severe laryngeal attack. • Patient must be able to identify the start time of the attack. • At least 48 hours have elapsed since patient has used conventional on--demand treatment or IMP to treat an HAE attack. • Patient must be able to complete at least the first 4 hours of eDiary assessments following the first administration of IMP. • Post-attack televisit has been completed for the previous eligible attack (applicable to eligible attacks 2 and 3 only). Eligible attacks should initially be treated with a single administration of IMP. Patients will be encouraged to treat as soon as possible after recognition of the start of the attack. If needed (as determined by the patient), a second dose of IMP may be administered for each attack, as follows: <u>Non-laryngeal attacks</u> For each eligible HAE attack, a second dose of IMP may be taken: • after **3** hours if HAE attack symptoms are considered severe enough by the patient to require a second dose of IMP. After the second dose of IMP, conventional on-demand treatment may be taken: • after **1** hour if HAE attack symptoms are considered severe enough by the patient to require treatment with conventional treatment. If symptoms progress to airway involvement, patients may treat with conventional on-demand treatment at any time. <u>Laryngeal attacks</u> After the first dose of IMP, conventional on-demand treatment may be taken at any time:

- if HAE attack symptoms worsen or if HAE attack symptoms are considered severe enough by the patient to require immediate treatment.

Attacks that do not meet eligibility may be treated with conventional on-demand treatment per the patient's usual treatment regimen.

Conventional on-demand treatments may include plasma derived C1-inhibitor (pdC1-INH) intravenous (iv), recombinant human C1-esterase inhibitor (rC1-INH) iv, icatibant subcutaneous (sc), or ecallantide sc.

Patients with safety or tolerability concerns will contact the Investigator or designee as soon as possible or the nearest emergency service as appropriate.

Study Call Center

After the first dose of IMP and prior to the second dose or conventional on-demand treatment, patients will be required to call a designated Study Call Center to be reminded of the repeat dosing criteria and the eDiary assessment requirements. Patients are to contact the Call Center:

1) After the first dose of IMP
2) Prior to a second dose of IMP
3) Prior to a dose of conventional on-demand treatment.

The Call Center staff will also instruct patients experiencing laryngeal attacks to call their study doctor.

Patient eDiary

For each HAE attack treated with IMP, patients will record information in an eDiary, including attack location, attack symptoms, date/time of onset, attack severity, time of second IMP dose, if applicable, and use of conventional on-demand treatment, if applicable. Patients will complete timed assessments of their HAE attack through 48 hours as documented in Table S1. Patients should complete all timed diary assessments except during sleep; however, patients must complete at least the first 4 hours of diary assessments following the first administration of IMP.

Table S1: Frequency of Patient Assessment

Time Period following the First IMP Administration	Frequency of Patient Assessment [a]	Time Window for Assessment
0 to 4 hours	Every 0.5 hour	± 0.25 hour
5 to 12 hours	Every 1 hour	± 0.5 hour
14 to 24 hours	Every 2 hours	± 1 hour
25 to 48 hours	Every 12 hours	± 3 hours

[a] If a second dose of IMP or additional doses of conventional on-demand treatment are needed, patients will complete diary assessments prior to taking each additional dose. After re-dosing, the planned post-dose diary assessments will then continue through 48 hours after first dose of IMP.

Post-Attack Televisit

A televisit (between the site staff and the patient) will be completed following each administration of IMP to ensure the safety and wellbeing of the patient, to confirm IMP accountability, to review the patient diary (and retrain, if necessary), and to undergo an AE and concomitant medication review. The televisit will occur by the next working day after the completion of the patient diary (visit window: +1 week).

	Final Visit/Early Termination Once 3 HAE attacks have been treated, or upon early termination, the patient should return to the clinic for the final visit as soon as possible within 1 week of completing all patient diary assessments to undergo final safety checks including AE reporting, vital sign recording, and blood sampling for laboratory safety measurements. Whenever possible, this visit should be completed prior to starting any new medication or treatment.
Investigational Medicinal Products	KVD900 (300 mg) film-coated tablet. Placebo for KVD900 tablet. No IMP dose modifications are allowed in this trial. Tablets must be swallowed whole and are not to be crushed or modified in any way. Eligible attacks should initially be treated with a single administration of IMP as soon as possible after recognition of the start of the attack. If needed (as determined by the patient), a second dose of IMP may be administered for each attack.
Number of Patients	Approximately 114 patients will be randomized into the trial to ensure approximately 84 patients (including approximately 12 adolescents) complete the trial.
Population	The trial population will include male and female patients 12 years of age and older with a confirmed diagnosis of HAE type I or II. The trial population will comprise 2 subsets: (1) patients who enter the trial taking only conventional on-demand treatment; and (2) patients who enter the trial on a stable dose and regimen of long-term prophylactic treatment. **Inclusion Criteria** 1) Male or female patients 12 years of age and older. 2) Confirmed diagnosis of HAE type I or II at any time in the medical history: a) Documented clinical history consistent with HAE (sc or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND EITHER i) Diagnostic testing results obtained prior to randomization that confirm HAE type I or II: C1-INH functional level <40% of the normal level. Patients with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Testing may be obtained from central or local laboratories or obtained from documented historical testing results. Patients may be retested at any time prior to randomization if results are incongruent with clinical history or believed by the Investigator to be confounded by recent prophylactic or therapeutic C1-INH use, OR ii) Documented genetic results that confirm known mutations for HAE type I or II. 3) Patient has access to and ability to use conventional on-demand treatment for HAE attacks. 4) If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must have been on a stable dose and regimen for at least 3 months prior to the Screening Visit (except for danazol, which requires a stable dose and regimen for 6 months prior to the Screening Visit). Patient must be willing to remain on a stable dose and regimen for the duration of the trial. 5) Patient's last dose of attenuated androgens other than danazol was at least

	28 days prior to randomization. 6) Patient: a) has had at least 2 documented HAE attacks within 3 months prior to screening or randomization; or b) is a completer of the KVD824-201 trial within 3 months prior to randomization and meets all other entry criteria to enroll in KVD900-301. 7) Patients must meet one of the following contraception requirements as follows: a) Female patients who are fertile and heterosexually active must agree to use contraception from the Screening Visit until the Final or Early Termination (ET) Visit. Acceptable methods of contraception include one or more of the following: i) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable (hormonal contraception that contains estrogen including ethinylestradiol is excluded per Exclusion Criterion 4). ii) Intrauterine device. iii) Intrauterine hormone–releasing system. iv) Bilateral tubal occlusion. v) Vasectomized partner (provided that the partner is the sole heterosexual partner of the female patient of childbearing potential and that the vasectomized partner has received medical assessment of surgical success). vi) Male or female condom. vii) Cap, diaphragm, or sponge with spermicide. b) Patients who are not fertile or not heterosexually active, as defined below, do not require contraception. If the patient's status changes during the course of the trial, they will be required to meet the requirements specified in Inclusion Criterion 7a). i) Female patients who refrain from heterosexual intercourse during the trial if the reliability of the heterosexual abstinence has been evaluated in relation to the duration of the clinical trial and is the preferred and usual lifestyle of the patient. ii) Female patients who are surgically sterile (e.g. status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months. iii) Female patients who are premenarche and remain premenarcheal until the end of the trial. c) Male patients (including female partners) do not require contraception. 8) Patients must be able to swallow trial tablets whole. 9) Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the eDiary. 10) Investigator believes that the patient is willing and able to adhere to all protocol requirements. 11) Patient provides signed informed consent or assent (when applicable). A parent or legally authorized representative must also provide signed informed consent when required.

	Exclusion Criteria 1) Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria. 2) A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. 3) Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit or within 7 days prior to randomization. 4) Any estrogen-containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Screening Visit. 5) Patients who require sustained use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers . Note: These medications include but are not limited to the following: **Inhibitors:** boceprevir, clarithromycin, cobicistat, dasabuvir, denoprevir, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole. **Inducers:** apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort. 6) Inadequate organ function, including but not limited to: a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN) b) Aspartate aminotransferase (AST) >2x ULN c) Bilirubin direct >1.25x ULN d) International normalized ratio (INR) >1.2 e) Clinically significant hepatic impairment defined as a Child-Pugh B or C. 7) Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial. 8) History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. 9) Known hypersensitivity to KVD900 or placebo or to any of the excipients. 10) Prior participation in trial KVD900-201. 11) Participation in any gene therapy treatment or trial for HAE. 12) Participation in any interventional investigational clinical trial (with the exception of KVD824-201), including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to Screening. 13) Any pregnant or breastfeeding patient.
Assessments	**Efficacy Variables** • Patient global impression of change (PGI-C) scored on a 7-point rating scale as much better, better, a little better, no change, a little worse, worse, much worse. • Patient global impression of severity (PGI-S) scored on a 5-point rating scale as none, mild, moderate, severe, and very severe. • Visual analog scale (VAS) anchored at 0 (none) and 100 (very severe) for abdominal pain, skin pain, and skin swelling.

	• Modified General Anxiety – Numeric Rating Scale (GA-NRS) scored on an 11-point scale anchored at 0 (not at all anxious) and 10 (extremely anxious). • Use of conventional on-demand treatment. **Safety Variables** • Adverse events, including serious adverse events. • Laboratory test results. • 12-lead ECG. • Vital signs. • Physical examination findings.
Criteria for Evaluation of Efficacy	**Primary Endpoint** • PGI-C: Time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of the first IMP administration. **Key Secondary Endpoints** • PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration. • PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration. **Secondary Endpoints** • PGI-C: Proportion of attacks with beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 4 hours and within 12 hours of the first IMP administration. • PGI-C: Time to at least "better" (2 time points in a row) within 12 hours of the first IMP administration. • PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration. • Composite VAS: Time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of the first IMP administration. **Exploratory Endpoints** • GA-NRS: Cumulative GA-NRS expressed as area under the curve over 12 and 24 hours of the first IMP administration.
General Statistical Methods and Types of Analyses	Continuous data will be summarized by treatment group using descriptive statistics (number, arithmetic mean, median, standard deviation, 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. There are 3 treatment groups in the trial: 1. 300 mg KVD900 2. 600 mg KVD900 3. Placebo for KVD900

	Two pairwise comparisons will be performed: 300 mg KVD900 versus placebo and 600 mg KVD900 versus placebo. Confirmatory efficacy analysis will be performed on the Full Analysis Set: A fixed sequence closed testing procedure will be followed. In a fixed sequence closed testing procedure the formal inferential testing can proceed to the next step only when statistical significance is declared in the current step. If the testing sequence is stopped, the remaining endpoints in the testing sequence will be considered exploratory. The fixed testing procedure will be employed first on the primary and then on the key secondary endpoints 1 and 2, separately for each dose comparison to placebo. Statistical tests on both the primary and the key secondary endpoints will be at the same significance level alpha (0.025) with a loop-back feature to allow two-way alpha passing. Significance level 0.025 is Bonferroni adjusted significance level obtained by dividing the original significance level 0.05 by the number of comparisons within endpoint family between each KVD900 dose level and placebo, i.e. the adjusted significance level is 0.025 (0.05 divided by 2). If the primary and key secondary endpoints hypotheses within one of the pairwise comparisons are not all rejected at 0.025 alpha level, but the hypotheses for the other pairwise comparison are all rejected, then the unused alpha from the rejected hypotheses can be directed to loop-back to the unrejected hypotheses, which is then re-tested at the alpha level of 0.05. The analysis of the secondary or exploratory endpoints will not have multiplicity adjustments. **Primary analysis hypothesis** The null hypothesis is that there is no difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP administration (no difference between each dose of KVD900 group versus placebo group) versus the alternative hypothesis that the survival distributions are different (each of the KVD900 dose groups versus placebo). $$H_0: t_k - t_p = 0,$$ where t_k is the time to “a little better” or higher rating of HAE attack following KVD900 dose treatment and t_p is the time to “a little better” or higher rating of HAE attack following placebo. $$H_a: t_k - t_p \neq 0.$$ The primary endpoint will be analyzed using Gehan Score Transformation test proposed by Feingold and Gillespie (1996) for crossover trials with censored data. The number of patients with the primary endpoint event will be summarized by frequencies and survival estimates, the summaries will be presented by treatment.

Table 1: Schedule of Events

Visit	Screening	Randomization[a]	Treatment Period			Final Visit/ET[c]
			1st eligible HAE attack[b]	2nd eligible HAE attack[b]	3rd eligible HAE attack[b]	
In-clinic[d]	X	X				X
TeleVisit[e]			X	X	X	
Informed Consent/Assent[f]	X					
Eligibility Assessment	X	X				
HAE Diagnostic Lab Test[g]	X					
Medical History[h]	X					
12-lead ECG[i]	X					X
Demographics[j]	X					
Physical Examination[k]	X					X
Vital Signs[l]	X					X
Safety Laboratory[m]	X					X
Pregnancy Test[n]	X					X
Randomize patient in RTSM		X				
Patient diary training	X	X				
Patient diary retraining			X	X	X	
Conventional on-demand treatment washout[o]			◄———	———	———►	
Dose[p]			X	X	X	
IMP dispensing/return/accountability[q]		X				X
PGI-S[r]			X	X	X	
PGI-C[r]			X	X	X	
VAS[r]			X	X	X	
GA-NRS[r]			X	X	X	
Concomitant Medication Review	◄———	———	———	———	———►	

Visit	Screening	Randomization[a]	Treatment Period			Final Visit/ET[c]
			1st eligible HAE attack[b]	2nd eligible HAE attack[b]	3rd eligible HAE attack[b]	
Adverse Event Review[s]	◄	———	———	———	———	►

Abbreviations: C1-INH=C1-esterase inhibitor; ECG=electrocardiogram; eDiary=electronic diary; ET=Early Termination; GA-NRS= General Anxiety – Numeric Rating Scale; HAE=hereditary angioedema; IMP=investigational medicinal product; PGI-C=patient global impression of change; PGI-S=patient global impression of severity; RTSM=Randomization Trial Supply Management System; VAS=visual analog scale.

a Randomization to occur within 4 weeks of the Screening Visit. The Randomization Visit may be a televisit or an in-clinic visit.

b For each of the 3 eligible HAE attacks, a televisit will occur by the next working day after the completion of the patient diary (visit window: +1 week). A televisit must occur before treating the next eligible attack.

c Once 3 HAE attacks have been treated with IMP, or upon patient ET, the patient should return to the clinic for the final visit as soon as possible within 1 week of completing all patient diary assessments. Whenever possible this visit should be completed prior to starting any new medication or treatment.

d If an in-clinic visit cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the patient from attending in-clinic visits), home health visits will be used to perform these visits. Information captured during a home health visit will mirror that captured during an in-clinic visit.

e A televisit can be conducted via a telephone call or via an interactive audio/video system.

f Consent and assent may be collected through e-consent if allowed through country and site regulations.

g Diagnostic testing must be available for patients without genetic confirmation of HAE type I or II.

h Medical history includes any relevant previous and concurrent diseases, HAE disease history including the attack history and corresponding treatment for the past 3 months; therapies and supplements taken within the past 4 weeks; and previous participation in interventional clinical trials in the past 4 weeks.

i ECG to be recorded after patient has rested supine for at least 5 minutes.

j Demographics: Year of birth; height (meters [m]; without shoes); weight (kilograms [kg]); race and ethnicity (if allowed); and sex.

k Complete physical examination at Screening only, all others will be symptom directed. In the case of a home health visit, the home healthcare nurse will conduct an abbreviated physical examination, and the Investigator will conduct the symptom-directed physical examination via televisit.

l Vital signs include pulse rate, respiratory rate, and systolic and diastolic blood pressure after patient has been resting at least 5 minutes.

m Laboratory assessments, including C1-INH functional level, performed by a central laboratory; repeat laboratory assessments may be performed.

n Serum pregnancy test will be performed on females of childbearing potential at Screening and at the Final/ET visit.

o If a patient takes conventional on-demand treatment during the trial, a 48-hour washout period is required prior to the subsequent dosing with IMP.

p Eligible attacks should be treated with IMP as soon as possible after recognition of the start of the attack. A minimum 48-hour washout period is required between each eligible attack and last dose of IMP or conventional on-demand treatment. After the first dose of IMP and prior to the second dose or conventional on-demand treatment, patients will be required to call a designated Study Call Center to be reminded of the repeat dosing criteria. The Call Center staff will remind patients of the rules for re-dosing and the eDiary assessment requirements.

q Arrangements will be made to dispense the assigned IMP. The IMP will be shipped to the patient via a courier service or will be dispensed at the trial clinic as required by local regulations or per the site's local practice, as described in the Pharmacy Manual. Confirmation of dosing compliance will be performed at each of the HAE attack televisits. All unused IMP and packaging will be returned at the in-clinic Final Visit/ET Visit. If the Final Visit/ET Visit is performed by Home Health, arrangements will be made to return any unused IMP and packaging via courier.

r Patients will complete timed assessments of HAE attack symptoms through 48 hours following first dose of IMP. Patient assessments will be performed as outlined in Table S1.

s Adverse events recorded from the first dose of KVD900 or placebo up to and including to Final Visit/ET. Serious AEs recorded from the time of signing the informed consent up to and including the Final Visit/ET.

4. KEY CONTACT LIST

Sponsor	KalVista Pharmaceuticals Ltd Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom [redacted] Vice President, Clinical Phone: [redacted] Email: [redacted]
Sponsor Medical Expert	[redacted] Chief Medical Officer Phone: [redacted] Email: [redacted]
Contract Research Organization	PPD Development, LP 929 North Front Street Wilmington, NC 28401 USA
Central Laboratory	PPD Laboratories US 2 Tesseneer Drive Highland Heights, KY 41067 USA
Medical Monitor	[redacted] PPD Serbia, Belgrade Phone: North America: [redacted] EMEA, APAC: [redacted]
Pharmacovigilance for SAE Reporting	SAE Reporting Email: [redacted] SAE Reporting Fax#: North America: [redacted] EMEA, APAC: [redacted]
All other contact details are located in trial-specific documentation.	

5. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	angiotensin-converting enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BR2	bradykinin receptor 2
C1-INH	C1-esterase inhibitor
CRO	Contract Research Organization
CYP3A4	cytochrome P450 3A4
DBP	diastolic blood pressure
eCRF	electronic case report form
eDiary	electronic diary
EC	Ethics Committee
ECG	electrocardiogram
ET	early termination
FAS	Full Analysis Set
GA-NRS	General Anxiety – Numeric Rating Scale
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HAE	hereditary angioedema
HbA1c	glycosylated hemoglobin
HCG	human chorionic gonadotropin
HED	human equivalent dose
HK	high molecular weight kininogen
HR	heart rate
IB	Investigator's Brochure

IcEv	intercurrent event
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
iv	intravenous
kg	kilogram(s)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
mL	milliliter(s)
ms	millisecond(s)
NOAEL	no-observed adverse effect level
pdC1-INH	plasma derived C1-inhibitor concentrate
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
pH	potential hydrogen
PK	pharmacokinetic
PPS	Per-protocol Set
PR	pulse rate
QTcF	Fridericia correction of QTc
RBC	red blood cell
RDW	red cell distribution width
rhC1-INH	recombinant human C1-esterase inhibitor
RR	respiration rate
RTSM	Randomization and Trial Supply Management System

s	second(s)
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
sc	subcutaneous
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USM	Urgent Safety Measure
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization

6. INTRODUCTION

6.1 Background

Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease caused by a deficiency in the C1-esterase inhibitor (C1-INH) protein and characterized by unpredictable tissue swelling due to an increase in vascular permeability. The prevalence of HAE ranges between 1 and 2 per 100,000 people worldwide with a point estimate of 1.5 per 100,000 (Aygören-Pürsün et al. 2018). HAE types I and II account for approximately 90% and 10% of HAE cases with C1-INH deficiency, respectively (Nordenfelt et al. 2016, Zanichelli et al. 2015). Both types of HAE are caused by a large variety of genetic mutations in the *SERPING1* gene (Gösswein et al. 2008). These mutations result in production of reduced levels of functional C1-INH (HAE type I) or normal levels of dysfunctional C1-INH (HAE type II) (Donaldson and Evans 1963, Donaldson and Rosen 1964, Rosen et al. 1965, Rosen et al. 1971).

C1-INH inhibits key enzymes in the contact system (Kaplan and Joseph 2014), one of which is plasma kallikrein. Due to the deficiency in C1-INH associated with HAE, activated plasma kallikrein generates the vasoactive peptide hormone bradykinin, the mediator of vascular hyperpermeability that causes tissue swelling and pain (Fields et al. 1983, Hulström and Svensjö 1979, Nussberger et al. 1998, Nussberger et al. 2002, Nussberger et al. 1999).

HAE is a life-long condition with approximately 50% of patients experiencing their first attack before the age of 10 years (Bork et al. 2006, Nordenfelt et al. 2016) and more than 75% experiencing their first attack before adulthood (Maurer et al. 2019). Attacks are episodic with considerable variations in frequency and severity (Bork et al. 2006, Javaud, Altar et al. 2019). Swelling has been shown to affect subcutaneous (sc) tissue (face, upper or lower extremities, genitals) in 82% of patients, abdominal organs (stomach, intestines) in 78% of patients, and the upper airway (larynx, tongue) in 27% of patients (Nordenfelt et al. 2016). Laryngeal attacks are infrequent (<5% of attacks) (Javaud, Altar et al. 2019) but are potentially life-threatening in patients who are unaware of their diagnosis (Bork et al. 2012). Approximately 50% of all patients with HAE experience at least one laryngeal attack during their lifetime (Bork et al. 2003, Bork et al. 2006).

Several precipitants can trigger HAE attacks; however, more than half of all HAE attacks are unpredictable and occur without an obvious trigger (Caballero et al. 2016). Common triggers of HAE attacks such as strenuous activity, mechanical trauma, or use of certain medications, may be somewhat predictable. However, other triggers such as infections, fatigue, or emotional stress are difficult to predict (Caballero et al. 2016). Although patients with HAE have been shown to have high health-related quality of life scores (Javaud, Bouillet et al. 2019, Lumry et al. 2018), physical and emotional impairment persists in their daily lives and may extend beyond the duration of the attacks (Aygören-Pürsün et al. 2016, Caballero et al. 2014, Nordenfelt et al. 2017).

6.2 Trial Rationale

Recurrent swelling in patients with HAE is predominantly a consequence of excessive generation of bradykinin due to dysregulated plasma kallikrein activity (Fields et al. 1983, Nussberger et al. 1998, 2002). Therefore, inhibition of plasma kallikrein activation has emerged as a target for the treatment of HAE. For example, treatment with ecallantide, a specific inhibitor of plasma kallikrein given subcutaneously, led to significantly better treatment outcome scores compared with placebo (Cicardi et al. 2010, Sheffer et al. 2011). The oral small-molecule inhibitor of plasma kallikrein berotralstat

(Aygören-Pürsün, Bygum et al. 2018, Zuraw et al. 2020) and the plasma kallikrein monoclonal antibody lanadelumab (Banerji et al. 2017, Banerji et al. 2018) have been shown to lower the rate of attacks in HAE patients compared with placebo, highlighting the role that plasma kallikrein plays in this disease.

KVD900 has been shown in a range of nonclinical experiments to be a selective inhibitor of plasma kallikrein. This activity was confirmed in a completed trial (KVD900-101) of KVD900 in healthy volunteers at dose levels up to 600 mg. Within 1 hour of dosing mean protection of high molecular weight kininogen (HK) cleavage was >85%. Protection was maintained at >75% for 6 hours and >45% for 10 hours at a dose of 600 mg. Forty percent (40%) HK protection is achieved by C1-INH levels typically present in control plasma samples. It is therefore a plausible hypothesis that treatment with a single dose of KVD900 600 mg may halt the progression of HAE attacks. This hypothesis was tested in a Phase 2 trial (KVD900-201) for the on-demand treatment of HAE attacks. The trial was a cross-over in which 53 patients with either type I or II HAE completed. Results showed a significant difference between 600 mg KVD900 and placebo for the primary endpoint of time to conventional treatment use and secondary endpoints of attack improvement using Patient Global Impression of Change (PGI-C), Patient Global Impression of Severity (PGI-S), and a composite visual analogue scale (VAS) measuring symptoms of the attack.

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

6.3 Benefit/Risk

Good Laboratory Practice repeat dose toxicology studies (rats and monkeys), genetic toxicology, safety pharmacology, and reproductive toxicology studies (rats and rabbits) have been completed. The non-clinical program is supportive of the included population and of the dosing regimen outlined in the trial.

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 a Phase 1 trial in healthy volunteers (KVD900-101) to have a time profile for plasma kallikrein inhibition (30 minutes to 10 hours post-dose) which is appropriate for the treatment of this condition. A single dose of 600 mg was found to bring relief from an attack of HAE in a single Phase 2 efficacy trial (KVD900-201). Key endpoints included the time to beginning of symptom relief using the PGI-C, the time to improvement using the PGI-S, the time to symptom relief in the composite VAS, and the time to conventional attack treatment usage. All key efficacy endpoints were met with $p<0.0064$. KVD900 reduced the time to patient-reported outcome on the PGI-C (1.6 hours vs. 9 hours, KVD900 vs. Placebo), PGI-S (9.0 hours vs. >24 hours, KVD900 vs. placebo), and the composite VAS (6 hours vs. 19 hours, KVD900 vs. placebo). Additionally, time to use of conventional attack treatment within 12 hours was significantly longer for KVD900 versus placebo (p-value=0.0010).

In the completed Phase 1 healthy volunteer trials and a Phase 2 trial in patients with type I or II HAE, single and multiple doses (up to three 600 mg doses within 24 hours) of KVD900 were well tolerated with no serious adverse events (SAEs) or deaths. A total of 104 healthy volunteers, across 3 clinical trials (KVD900-101, KVD900-102, KVD900-103) were administered KVD900 and 28 were administered placebo, and of those volunteers, 32.7% and 35.7%, experienced at least 1 adverse event (AE), respectively. The most common AE was headache, which occurred in 7.7% and 7.1% of healthy volunteers administered KVD900 and placebo, respectively.

In the blinded portion of the Phase 2 trial (KVD900-201) completed in patients with type I or II HAE, at least 1 AE while on treatment was deemed by the Investigator to be related to the investigational medicinal product (IMP) and was reported for 3 of 58 patients (5.2%) administered KVD900 (AEs of abdominal pain, back pain, and headache) and 2 of 55 patients (3.6%) administered placebo (AEs of anal incontinence and headache).

A completed multiple dose trial of 600 mg KVD900 in healthy normal volunteers (KVD900-102) assessed the pharmacokinetic (PK) and changes to cardiac parameters of 600 mg KVD900 given every 2 hours for 3 total administrations (i.e. 1,800 mg KVD900 within 4 hours). Safety evaluation did not identify any clinically significant changes in vital signs, safety electrocardiogram (ECG), physical exam finding, or laboratory results approximately 24 hours post-dose as well as 5 to 7 days post dose. There were no clinically meaningful AEs with the most common AE being headache. Furthermore, an analysis of the impact of KVD900 on heart rate (HR) and QTc showed no clinically meaningful changes to HR or QTc (defined as >10 ms increase) following supratherapeutic concentrations of KVD900.

The current trial (KVD900-301) will evaluate two dose levels of KVD900 (with the option for patients to take a second dose of IMP to treat each attack) for the on-demand treatment of HAE attacks under randomized, double-blind, placebo-controlled conditions. E*x vivo* testing suggests that a dose of 300 mg may also bring relief to an attack of HAE. The randomized, double-blind, placebo-controlled, three-way crossover design of this trial has been chosen as an appropriate test of that hypothesis.

Adolescents (12 to 17 years old) will be included in this trial. A population PK model has been built which predicted KVD900 exposure in a simulation population containing 600 subjects (400 females and 200 males) 12 to 17.9 years of age with body weight ranging from 31.0 to 93.3 kg. The population PK model predicted overall KVD900 exposure in an adolescent population (12 to 17 years old) to be similar to that in healthy adults for a single 600 mg dose of KVD900 under fasted conditions.

While laryngeal attacks may be treated in KVD900-301, only mild and moderate attacks will be allowed, and patients will be instructed to treat immediately with conventional on-demand treatment if laryngeal attack symptoms worsen.

For a subset of the trial population, the trial permits the use of HAE prophylaxis therapies as detailed in Section 12.1. Given the difference in clearance mechanisms between KVD900 and allowed HAE prophylaxis treatment (lanadelumab; C1-INH) it is not anticipated that KVD900 would cause drug-drug interactions with these medications. The potential for these medications to affect the PK of small molecules such as KVD900 is generally limited to proinflammatory cytokines or that cause increases in proinflammatory cytokine levels (FDA Guidance for Industry, Drug-Drug Interaction Assessment for Therapeutic Proteins, 2020). The prophylaxis treatments allowed do not fall into these categories, and therefore it is not anticipated that the PK profiles of KVD900 or the allowed HAE prophylactic treatments would be impacted (European Medicines Agency, Takhzyro ([lanadelumab] Assessment Report, 2018). As androgens and anti-fibrinolytics are not strong inducers or inhibitors of CYP3A4, it is not anticipated that they would affect the PK profile of KVD900. Likewise, given the relatively weak CYP450 *in vitro* inhibition and induction elicited by KVD900, and the various clearance mechanisms of androgens and anti-fibrinolytics, it is not expected that KVD900 would notably affect the PK of these agents. Based on available data on berotralstat and KVD900, it is assumed that co-administration with KVD900 would have little to no impact on the PK of berotralstat. Data have shown an increase of 45% and 124% in C_{max} and AUC, respectively, of midazolam (a prototypical cytochrome P450 3A4 [CYP3A4] substrate) with co-administration of berotralstat (BioCryst Pharmaceuticals, Inc, 2020). KVD900 is not expected to be a

more sensitive CYP3A4 substrate than midazolam; therefore, a similar increase in C_{max} and AUC can be assumed. An increase in exposure to this magnitude would not be a clinically significant increase for KVD900.

Overall, trial KVD900-301 is considered to have a positive benefit-risk balance given that:

- Inhibition of plasma kallikrein is an established mechanism for the treatment of HAE. There are currently approved plasma kallikrein inhibitors that do not have known target-related AEs.
- Non-clinical studies support the dosing regimen and also the inclusion of women of child-bearing potential.
- Pharmacological data indicate that doses of 300 or 600 mg may be effective to bring relief to an attack of HAE. The high dose level of KVD900 to be given in this trial, 600 mg, was well tolerated in previous clinical trials in 104 healthy volunteers and 68 patients with type I or II HAE.
- Administration of up to 3 doses of 600 mg KVD900 administered 2, 4, or 8 hours apart was well tolerated in KVD900-102 and supports the planned dosing regimen in this trial of up to 2 doses for HAE attack treatment.
- 600 mg KVD900 was shown to be efficacious and significantly different from placebo in time to conventional treatment use and symptom improvement in the PGI-C, PGI-S, and composite VAS in patients with type I or II HAE in the Phase 2 clinical trial (KVD900-201).

6.3.1 Impact of COVID-19 on Benefit-Risk Assessment

Significant suppression of plasma kallikrein activity exists as a genetic condition (prekallikrein deficiency) (Girolami et al. 2010) and through therapeutic intervention with, for example, lanadelumab, a monoclonal antibody against plasma kallikrein (Banerji et al. 2018). Neither the familial condition nor administration of lanadelumab in patients with HAE is known to increase susceptibility to viral infections or lead to increased infections in general. Also, epidemiological studies among patients with HAE have not shown increased risks of infections (Zanichelli et al. 2015). At present, plasma kallikrein inhibition with KVD900 is unlikely to confer susceptibility or aggravation of symptoms to infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

6.3.2 COVID-19 Vaccination

There are no known risks or expected interaction with KVD900 and COVID-19 vaccines. Patients may receive an approved COVID-19 vaccine, i.e. a vaccine that has received Emergency Use Authorization/Conditional Marketing Authorization (or approved/licensed) before, during, or after being in this trial. When feasible, the full vaccination series should be completed prior to enrollment. If a patient participated in an investigational COVID-19 vaccine trial, 4 weeks after the last dosing should elapse prior to Screening.

7. OBJECTIVES AND ENDPOINTS

7.1 Objectives

7.1.1 Primary

The primary objective of this trial is to demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.

7.1.2 Secondary

The secondary objective of this trial is to investigate the safety and tolerability of KVD900.

7.2 Endpoints

7.2.1 Primary Endpoint

The primary endpoint of this trial is:

- PGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration.

7.2.2 Key Secondary Endpoints

Key secondary endpoints of this trial are:

- PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration.
- PGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration.

7.2.3 Secondary Endpoints

The secondary endpoint of this trial are:

- PGI-C: Proportion of attacks with beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 4 hours and within 12 hours of the first IMP administration.
- PGI-C: Time to at least “better” (2 time points in a row) within 12 hours of the first IMP administration.
- PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 24 hours of the first IMP administration.
- Composite VAS: Time to at least a 50% decrease from baseline (3 time points in a row) within 12 hours and within 24 hours of the first IMP administration.

7.2.4 Exploratory Endpoints

- General Anxiety Numeric Rating Scale (GA-NRS): Cumulative GA-NRS expressed as area under the curve (AUC) over 12 and 24 hours of the first IMP administration.

Additional endpoints may be defined in the SAP.

7.3 Estimands

Table 2: Primary Objective and Estimand

Objective Description	Estimand Description (Including Endpoint)
To demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.	Relative effect of each of the KVD900 dose groups versus placebo in shortening the time to beginning of symptom relief defined by the PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP administration in adolescent and adult patients with hereditary angioedema type I or II regardless of prohibited medications and as long as conventional on-demand treatment of HAE attacks had not been used and as if patients had not discontinued the trial.

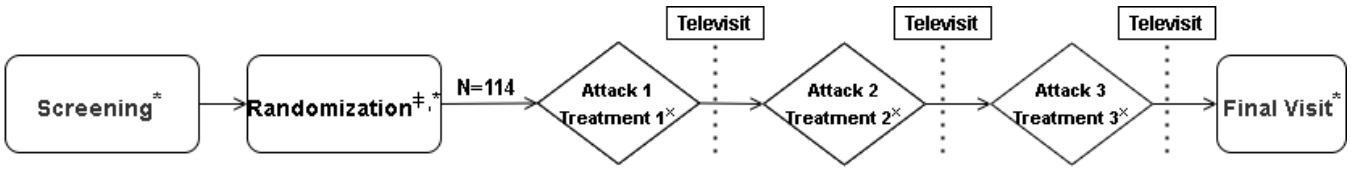
8. TRIAL DESIGN

8.1 Overall Design

KONFIDENT is a double-blind, randomized, placebo-controlled, multicenter clinical trial in patients 12 years or older with HAE type I or II. Patients will be randomized to 6 treatment sequences in a 3-way crossover design. Eligible attacks will initially be treated with a single dose of placebo, 300 mg, or 600 mg KVD900 per attack with a minimum 48-hour washout period between each eligible attack and last dose of IMP or conventional on-demand treatment. If needed (as determined by the patient), a second dose of IMP may be administered for each attack (for further detail, see Section 10.1).

The estimated duration of this trial for each randomized patient will be approximately 25 weeks from Screening through the Final Visit and includes the treatment of 3 eligible attacks during the Treatment Period.

This trial will be conducted at HAE treatment centers on an outpatient basis and will comprise in-clinic and televisits. A televisit can be conducted via a telephone call or via an interactive audio/video system. If an in-clinic visit cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the patient from attending the in-clinic visit) home health visits will be used to perform these visits if permitted by the relevant regulatory authority, site's Ethics Committee (EC)/ Institutional Review Board (IRB), local regulations, and the patient via informed consent. The home visit will be performed by an appropriately delegated home healthcare service provider. Information captured during a home health visit will mirror that captured in an in-clinic visit. A trial diagram is presented in Figure 1.



*If in-clinic visits are not possible (eg, in the event of a pandemic, or other reasons that prevent the patient from attending in-clinic visits), home health visits will be permitted in place of in-clinic visits. Information captured during a home health visit will mirror that captured in an in-clinic visit.

‡The Randomization Visit may occur as a televisit or in-clinic visit.

×Patients are to contact a call center after the initial dose of IMP, prior to a second dose of IMP, and prior to a dose of conventional on-demand treatment for each treated attack.

Figure 1: Trial Diagram

8.2 Scientific Rationale for Trial Design

This Phase 3 trial will investigate the efficacy of two dose levels of KVD900 in the on-demand treatment of attacks of HAE. The randomized, placebo-controlled, 3-way crossover trial design is a standard approach for differentiation between the efficacy and safety profiles of multiple dose levels of IMP and placebo treatments when administered to patients with HAE type I or II.

The trial population is representative of the likely target population for the product. The sample size of approximately 114 randomized patients to ensure approximately 84 completed patients (including approximately 12 adolescents) is required to conclusively evaluate a clinically relevant treatment effect. Treatment of three separate eligible HAE attacks with IMP and placebo is adequate to assess the primary and secondary objectives of the trial.

The high dose level of KVD900 to be given in this trial, 600 mg, was well tolerated in previous Phase 1 and Phase 2 clinical trials. Refer to the IB for further detail on completed KVD900 clinical trials.

A lower single dose of 300 mg may be reasonably expected to bring relief to or halt the progression of an attack of HAE.

The endpoints for this trial are commonly measured in HAE and are clinically relevant. The safety measures are routinely used for the evaluation of safety and tolerability of an investigational product.

8.3 Justification for Dose

Up to 2 doses of KVD900 (300 and 600 mg) per eligible HAE attack administered at least 3 hours apart is supported by the *ex-vivo* pharmacodynamic bioactivity, PK, safety, and efficacy of KVD900 from previous clinical trials and nonclinical studies that found KVD900 to be well tolerated and to result in pharmacodynamic effects with the potential to deliver clinical efficacy (see the KVD900 IB for further details).

8.4 End of Trial Definition

The end of this trial is defined as the last patient's last visit.

9. TRIAL POPULATION

HAE treatment centers worldwide will randomize approximately 114 patients into the trial to ensure approximately 84 patients (including approximately 12 adolescents) complete the trial.

The trial population will include a subset of patients who enter the trial taking only conventional on-demand treatment, and a subset of patients who enter the trial on a stable dose and regimen of long-term prophylactic treatment.

9.1 Inclusion Criteria

1) Male or female patients 12 years of age and older.
2) Confirmed diagnosis of HAE type I or II at any time in the medical history:
   a) Documented clinical history consistent with HAE (sc or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND EITHER
      i) Diagnostic testing results obtained prior to randomization that confirm HAE type I or II: C1-INH functional level <40% of the normal level. Patients with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Testing may be obtained from central or local laboratories or obtained from documented historical testing results. Patients may be retested at any time prior to randomization if results are incongruent with clinical history or believed by the Investigator to be confounded by recent prophylactic or therapeutic C1-INH use, OR
      ii) Documented genetic results that confirm known mutations for HAE type I or II.
3) Patient has access to and ability to use conventional on-demand treatment for HAE attacks.
4) If a patient is receiving long-term prophylactic treatment with one of the protocol-allowed therapies, they must have been on a stable dose and regimen for at least 3 months prior to the Screening Visit (except for danazol, which requires a stable dose and regimen for 6 months prior to the Screening Visit). Patient must be willing to remain on a stable dose and regimen for the duration of the trial.
5) Patient's last dose of attenuated androgens other than danazol was at least 28 days prior to randomization.
6) Patient:
   a) has had at least 2 documented HAE attacks within 3 months prior to screening or randomization; or
   b) is a completer of the KVD824-201 trial within 3 months prior to randomization and meets all other entry criteria to enroll in KVD900-301.
7) Patients must meet one of the following contraception requirements as follows:
   a) Female patients who are fertile and heterosexually active must agree to use contraception from the Screening Visit until the Final or Early Termination (ET) Visit. Acceptable methods of contraception include one or more of the following:
      i) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable (hormonal contraception that contains estrogen including ethinylestradiol is excluded per Exclusion Criterion 4).
      ii) Intrauterine device.

iii) Intrauterine hormone–releasing system.
iv) Bilateral tubal occlusion.
v) Vasectomized partner (provided that the partner is the sole heterosexual partner of the female patient of childbearing potential and that the vasectomized partner has received medical assessment of surgical success).
vi) Male or female condom.
vii) Cap, diaphragm, or sponge with spermicide.

b) Patients who are not fertile or not heterosexually active, as defined below, do not require contraception. If the patient's status changes during the course of the trial, they will be required to meet the requirements specified in Inclusion Criterion 7a).
i) Female patients who refrain from heterosexual intercourse during the trial if the reliability of the heterosexual abstinence has been evaluated in relation to the duration of the clinical trial and is the preferred and usual lifestyle of the patient.
ii) Female patients who are surgically sterile (e.g. status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months.
iii) Female patients who are premenarche and remain premenarcheal until the end of the trial.

c) Male patients (including female partners) do not require contraception.

8) Patients must be able to swallow trial tablets whole.
9) Patients, as assessed by the Investigator, must be able to appropriately receive and store IMP, and be able to read, understand, and complete the electronic diary (eDiary).
10) Investigator believes that the patient is willing and able to adhere to all protocol requirements.
11) Patient provides signed informed consent or assent (when applicable). A parent or legally authorized representative must also provide signed informed consent when required.

9.2 Exclusion Criteria

1) Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1-inhibitor deficiency, HAE with normal C1-INH (previously known as HAE type III), idiopathic angioedema, or angioedema associated with urticaria.
2) A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator.
3) Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit or within 7 days prior to randomization.
4) Any estrogen-containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Screening Visit.
5) Patients who require sustained use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers.

Note: These medications include but are not limited to the following:

Inhibitors: boceprevir, clarithromycin, cobicistat, dasabuvir, denoprevir, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir ombitasvir, paritaprevir,

posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole.

Inducers: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort.

6) Inadequate organ function, including but not limited to:
   a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
   b) Aspartate aminotransferase (AST) >2x ULN
   c) Bilirubin direct >1.25x ULN
   d) International normalized ratio (INR) >1.2
   e) Clinically significant hepatic impairment defined as a Child-Pugh B or C.
7) Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial.
8) History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator.
9) Known hypersensitivity to KVD900 or placebo or to any of the excipients.
10) Prior participation in trial KVD900-201.
11) Participation in any gene therapy treatment or trial for HAE.
12) Participation in any interventional investigational clinical trial (with the exception of KVD824-201), including an investigational COVID-19 vaccine trial, within 4 weeks of the last dosing of investigational drug prior to Screening.
13) Any pregnant or breastfeeding patient.

10. INVESTIGATIONAL MEDICINAL PRODUCT

For clinical trial use, KVD900 has been formulated as 300 mg film-coated tablets.

The active ingredient in the tablets is KVD900.

Further information about KVD900 300 mg film-coated tablets and matching placebo can be found in the IB.

10.1 Investigational Medicinal Product Administration

Patients will be assigned to receive the following three treatments in randomized, double-dummy blinded, crossover fashion to treat three separate eligible HAE attacks:

- 300 mg KVD900 (1 x 300 mg tablet plus 1 matching placebo tablet)
- 600 mg KVD900 (2 x 300 mg tablets)
- Placebo for KVD900 (2 matching placebo tablets)

For an HAE attack to be considered eligible for treatment with IMP, the attack must meet the criteria specified in Section 16.3. Attacks that do not meet eligibility may be treated with conventional on-demand treatment per the patient's usual treatment regimen.

Patients will treat each eligible attack with up to 2 doses of IMP, administered at least 3 hours apart. The second dose, if taken, will be the same assigned treatment as the first dose.

Patients will initially self-administer a single dose of KVD900 300 mg (1 x 300 mg tablet plus 1 placebo tablet), 600 mg (2 x 300 mg tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), a second dose of IMP may be administered for each attack (for details, see Section 16.3).

The post-attack televisit should be scheduled as soon as possible following IMP intake and completion of eDiary assessments. Patients with safety or tolerability concerns will contact the Investigator or designee as soon as possible or the nearest emergency service as appropriate.

The IMP will be shipped directly to the patient via a courier service or can be dispensed on site as required by local regulations or per the site's local practice, as described in the Pharmacy Manual. Patients will be provided with instructions on IMP administration.

No IMP dose modifications are allowed in this trial.

10.2 Packaging and Labeling

The investigational products (i.e. KVD900 or placebo) will be packaged and labeled according to current International Council for Harmonisation (ICH) Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and national legal requirements. The IMP will be packaged in appropriately labeled polyvinyl chloride/polyethylene/polyvinylidene chloride blisters sealed with an aluminum foil lid. The

blisters will be set into cardboard drawers contained in a cardboard cassette. The drawers will be numbered from 1 to 3, intended to be used in numerical order, one drawer per attack.

Patients will be provided with instructions concerning the dosing and storage of the IMP at home.

10.3 Storage and Drug Accountability

Prior to receipt by the patient, IMP will be stored at room temperature as labeled.

IMP will only be dispensed to the identified patients of this trial following the procedures described in Pharmacy Manual. All supplies of the investigational products must be accounted for at the end of the trial. Qualified site personnel will inventory IMP at each televisit and at the Final/ET Visit.

IMP that has been dispensed to a patient and returned unused must not be re-dispensed for a different patient. Unused IMP must not be used for any purpose other than the present trial.

After completion of the trial and following Sponsor approval, all unused IMP will either be returned to the Sponsor or designee for destruction. IMP may also be destroyed on site after Sponsor approval.

10.4 Trial Medication Compliance

Patients will be provided with instructions on IMP administration. In addition, confirmation of dosing compliance will be performed during each televisit (via review of unused IMP), and re-training will occur, if necessary. If the in-clinic visits cannot occur for the Final Visit/ET the accountability will occur during the home health visit, and arrangements will be made to return any unused IMP.

11. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

11.1 Patient Numbers Identification

Each patient will receive a unique patient identification number.

11.2 Randomization Scheme

Within 4 weeks of the Screening Visit, patients will participate in a Randomization Visit. Patients will be assigned to receive 3 treatments in randomized crossover fashion based on their assignment to 1 of 6 treatment sequences. Randomization will be stratified by whether the patient enters the trial taking only conventional on-demand treatment vs. on a stable dose and regimen of long-term prophylactic treatment.

Randomization will occur using a Randomization and Trial Supply Management System (RTSM) in a 1:1:1:1:1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment sequence. A sample randomization schedule is presented in Table 3.

Table 3: Sample Randomization Schedule

Treatment Sequence	1st Eligible HAE Attack	2nd Eligible HAE Attack	3rd Eligible HAE Attack
A	Placebo	600 mg	300 mg
B	Placebo	300 mg	600 mg
C	300 mg	600 mg	Placebo
D	300 mg	Placebo	600 mg
E	600 mg	300 mg	Placebo
F	600 mg	Placebo	300 mg

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

11.3 Blinding

This trial will be performed in a double-blind, double-dummy manner.

The trial blind should not be broken except in a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g. for SAEs or death). The patient's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded. The decision to break the trial blind will be made solely by the Investigator. Efforts should be made to contact the Sponsor and the Medical Monitor prior to breaking the blind.

Before breaking the blind of an individual patient's treatment, the Investigator should determine that the unblinded information is necessary, i.e. that it will alter the patient's immediate management. In many cases, particularly when the emergency is clearly not related to the IMP, the problem may be properly managed by assuming that the patient is receiving active product. Refer to the Medidata Rave RTSM and RAVE Electronic Data Capture Overview Training Material for the process to break blind.

Following the unblinding of the IMP for a patient, the Investigator should inform the Sponsor and Medical Monitor. In addition to this, the date, time, and reason for unblinding must be recorded.

If an Investigator, site personnel performing assessments, or patient, is unblinded, it must be documented as a 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 into the database and all data queries have been resolved and the assignment of patient to the analysis sets has been completed.

12. PERMITTED THERAPIES AND PROHIBITED THERAPIES

12.1 Conventional On-Demand Treatment

Conventional on-demand treatment is permitted as outlined in Section 16.3. Attacks that are not treated with IMP may be treated with conventional on-demand treatment per the patient's usual treatment regimen.

Conventional on-demand treatments include plasma derived C1-inhibitor (pdC1-INH) iv, recombinant human C1-esterase inhibitor (rC1-INH) iv, icatibant sc, or ecallantide sc.

12.2 Long- and Short-term Prophylactic Treatment

Patients who enter the trial using long-term prophylactic treatment must be on a stable dose and regimen for at least 3 months prior to the Screening Visit and remain stable during participation in the trial. Patients who do not enter the trial on a stable dose and regimen for at least 3 months prior to the Screening Visit will not be permitted to use long-term prophylactic treatment. They may use C1-INH as an on-demand or short-term prophylactic treatment but not as a long-term prophylactic treatment during the trial.

The following long-term prophylactic therapies for HAE are allowed during the trial:

- iv or sc plasma-derived C1-INH
- Lanadelumab
- Berotralstat
- Danazol (requires a stable dose and regimen for at least 6 months prior to the Screening Visit)

Note: In the event a patient takes conventional on-demand treatment or short-term prophylaxis during the trial, a 48-hour washout period is required prior to the subsequent dosing with IMP.

12.3 Prohibited Therapies

Medications and therapies that preclude a patient from enrolling in the trial are listed in Section 9.2.

The following therapies are not permitted for any patients during the trial:

- Attenuated androgens other than danazol (e.g. stanozolol, oxandrolone, methyltestosterone, testosterone)
- Anti-fibrinolytics (e.g. tranexamic acid)
- Other investigational therapies for HAE prophylaxis (e.g. garadacimab, PKK-LRx, PHVS416)
- ACE inhibitors
- Estrogen-containing medications with systemic absorption including:
    - Oral contraceptives including ethinylestradiol or hormonal replacement therapy
- Sustained use of strong CYP3A4 inhibitors and inducers (see Section 9.2 [Exclusion Criterion 5)] for list of trial medications)

- If use of a CYP3A4 inhibitor or inducer is required for treatment of a medical condition during the trial, IMP use should be discontinued and may not be re-started until 5 half-lives have elapsed since stopping the CYP3A4 inhibitor or inducer. Conventional on-demand treatment may be used while the patient is using the CYP3A4 inhibitor or inducer.

Details of all medications, therapies, and supplements administered within 4 weeks prior to the Screening Visit until the end of the trial will be recorded in the electronic case report form (eCRF). Prior medications are defined as those medications taken within 4 weeks prior to the Screening Visit up to the first dose of IMP; concomitant medications are defined as those medications ongoing at or started after the first dose of IMP.

13. PATIENT DISCONTINUTION

Patients may withdraw their consent from the trial at any time at their own request for any reason without prejudice to their medical care. If a patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

The patient also may be discontinued at any time by the Investigator for any of the following reasons:

- AEs.
- At the discretion of the Investigator.
- Administrative reasons (e.g. lack of patient compliance to trial visits/procedures, lost to follow-up).

If a patient is discontinued from the trial, every attempt will be made to complete and document the ET visit as soon as possible. If the patient is discontinued from the trial after receiving IMP, every effort will be made to ensure that the relevant safety assessments are completed. The patient may also be asked by the Investigator to complete other trial assessments. Patients who prematurely discontinue from the trial will continue to have access to medical care and will be treated as per routine medical practice.

The reason for and date of discontinuation will be recorded (e.g. withdrawal of consent, lost to follow-up, discontinuation due to an AE). If the reason for discontinuation is the occurrence of an AE, the patient will be followed up until the AE has resolved or is considered chronic or stable or the AE has been clearly shown to be unrelated to the IMP.

Discontinued patients will not be replaced; patient/randomization numbers will not be reused. If a patient does not complete a scheduled visit, every effort should be made to contact the patient to reschedule the visit. All efforts should be documented in the patient’s medical source record. A patient will be considered lost to follow-up if patient cannot be reached after 4 weeks from the scheduled visit.

14. ASSESSMENTS

The following assessments will be performed and recorded in the eCRF. The Schedule of Events by Visit is displayed in Table 1.

14.1 Patient Demographics and Medical History

Demographic and baseline data will include year of birth, height (meters [m]; without shoes), weight (kg), race and ethnicity (if allowed), and sex.

Medical history will capture any relevant previous and concurrent diseases, HAE disease history including the attack history and corresponding treatment for the past 3 months; therapies and supplements taken within the past 4 weeks; and participation in interventional clinical or COVID-19 trials in the past 4 weeks.

14.2 Efficacy Assessments

Efficacy variables of interest in this trial are:

- Change in overall HAE attack symptoms assessed using the PGI-C, scored on a 7-point rating scale 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 trial medication?
- Time of conventional on-demand treatment use captured in the patient diary.
    - What time did you take your conventional HAE attack medication?
- Overall HAE attack severity assessed on the PGI-S scored on a 5-point rating scale as none, mild, moderate, severe, very severe.
    - What is your overall HAE attack severity right now?
- The type of HAE attack symptoms (abdominal pain, skin pain and skin swelling) each assessed on a 101-point VAS anchored at 0 (none) and 100 (very severe).
    - How much abdominal pain/skin pain/skin swelling are you experiencing right now?
- Current anxiety level assessed on the Modified GA-NRS using an 11-point scale anchored at 0 (not at all anxious) and 10 (extremely anxious).
    - How anxious do you feel right now?

For each HAE attack treated with IMP, patients will record information in an eDiary, including attack location, attack symptoms, date/time of onset, attack severity, time of second IMP dose, if applicable, and use of conventional on-demand treatment, if applicable. Patients will complete timed assessments of their HAE attack through 48 hours as documented in Table 4. Patients should complete all timed diary assessments except during sleep; however, patients must complete at least the first 4 hours of diary assessments following the first administration of IMP.

Table 4: Frequency of Patient Assessment

Time Period following the First IMP Administration	Frequency of Patient Assessment [a]	Allowed Time Window for Assessment
0 to 4 hours	Every 0.5 hours	± 0.25 hour
5 to 12 hours	Every 1 hour	± 0.5 hour
14 to 24 hours	Every 2 hours	± 1 hour
25 to 48 hours	Every 12 hours	± 3 hours

IMP=investigational medicinal product

[a] If a second dose of IMP or additional doses of conventional on-demand treatment are needed, patients will complete diary assessments prior to taking each additional dose. The planned post-dose diary assessments will then continue according to the table after re-dosing. Patients will also be required to call a designated Study Call Center (for details and timing, see Section 16.3.1).

14.3 Safety Assessments

14.3.1 Physical Examinations

A physical examination will be performed by the Investigator or his/her qualified designee according to the Schedule of Events (Table 1). A complete physical examination will be performed at Screening only and will include the following body systems: general appearance; ears, nose, and throat; head and neck; ophthalmological; respiratory; cardiovascular; abdomen; neurological; extremities; dermatological; and lymphatic. Other visits noted in the Schedule of Events (Table 1) will include a symptom-directed physical examination.

In the case of a home health visit, the home healthcare nurse will conduct an abbreviated physical examination, and the Investigator will conduct the symptom-directed physical examination via televisit.

14.3.2 Vital Signs

Vital signs will be assessed after the patient has been at rest for at least 5 minutes in accordance with the Schedule of Events (Table 1). Vital signs will include blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]; mmHg), pulse rate (PR; beats per minute), and respiration rate ([RR] breaths per minute).

14.3.3 12-Lead Electrocardiogram

A 12-lead ECG will be recorded after the patient has rested supine for at least 5 minutes in accordance with the Schedule of Events (Table 1). Heart rate (beats per minute), PR-interval (milliseconds [ms]), QRS-duration (ms), QT-interval (ms) and RR-interval (seconds [ms]) will be recorded; QTcF (Fridericia correction of QTc; ms) calculated as per standard practice.

14.3.4 Clinical Safety Laboratory Assessments

Blood samples (approximately 40 mL) will be taken using standard venipuncture techniques. The central laboratory will provide a Laboratory Manual with detailed procedures. Safety labs (Table 5) will be collected per the Schedule of Events (Table 1).

Table 5: Laboratory Assessments

Hematology:	RBC MCV MCH MCHC MPV RDW Nucleated RBC WBC Neutrophils Eosinophils Basophils Lymphocytes Monocytes Platelets Granulocytes Hemoglobin Hematocrit	Urinalysis:	pH Protein Glucose Ketone Bilirubin Blood Nitrite Albumin Reflex to microscopic panel, as required
Clinical chemistry:	HbA1c Creatinine Glucose (Random) Triglycerides Urea, Blood Nitrogen Bilirubin, Total Bilirubin, Direct Cholesterol, Total	Liver enzymes:	ALP AST ALT GGT
Electrolytes:	Sodium Potassium	Coagulation	INR
C1 Functional Level:	C1-Esterase Inhibitor Activity		
C1 Antigen:	C1-Esterase Inhibitor Protein		
Complement C4:	Complement C4		
Pregnancy test (serum):	In female patients of childbearing potential. HCG Qualitative and Quantitative		

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HbA1c=glycosylated hemoglobin; GGT=gamma glutamyl transferase; HCG=human chorionic gonadotropin; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MCHC=mean corpuscular hemoglobin concentration; MPV=mean platelet volume; pH=potential hydrogen; RBC=red blood cell; RDW=red cell distribution width; WBC=white blood cell differential, immature granulocytes.

The Investigator must review screening laboratory results for patient eligibility prior to randomizing the patient. Laboratory tests may 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. Repeat laboratory assessments may be performed.

15. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

15.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs will be recorded from the first dose of IMP up to and including the Final Visit/ET. Any non-serious AEs occurring prior to the first dose of IMP should be recorded as medical history.

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. If an AE increases in severity it will be recorded as a new AE. Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to the IMP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon questioning.

HAE attacks will not be considered AEs unless they are considered SAEs.

15.2 Serious Adverse Events

Any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other).

SAEs will be recorded from the time of signing the informed consent up to and including the Final Visit/ET.

15.3 Time Period and Frequency for Collection

The period of observation for AEs extends from the time of the patient's first dose of IMP until the Final/ET Visit. Ongoing AEs at the Final/ET Visit will be followed up until the AE has resolved or is considered chronic or stable or the AE has been clearly shown to be unrelated to the IMP. The period of observation for SAEs extends from the time of signing the informed consent until the Final/ET Visit.

15.4 Method of Detection

All AEs spontaneously reported by the patient and/or in response to an open question from trial personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded.

15.5 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 patient. The assessment of severity is made irrespective of relationship to IMP or seriousness of the event and should be evaluated according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (US Department of Health and Human Services, 2007) where possible:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life-Threatening (Grade 4)

15.6 Relationship

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

- Related: A reasonable possibility exists that the IMP caused the AE.
- Not related: A reasonable possibility does not exist that the IMP caused the AE.

“Reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE.

Types of evidence that would suggest a causal relationship between the IMP and the AE include: A single occurrence of an event that is uncommon and known to be strongly associated with IMP exposure (e.g. hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IMP exposure, but is otherwise uncommon in the population exposed to the IMP (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 trial population independent of drug therapy) that indicates those events occur more frequently in the IMP group than in a concurrent or historical control group.

15.7 Reporting

15.7.1 Reporting AEs to EC/IRB and Regulatory Authorities

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

The Sponsor, or its designee, will inform Investigators, central ECs/IRBs and Regulatory Authorities of applicable safety reports, as required.

15.7.2 Reporting Serious Adverse Events or Urgent Safety Measures

Urgent Safety Measures (USMs) are procedures that may be undertaken by the Sponsor or the Investigator to protect a research patient from an immediate hazard to their health or safety. USMs can

be implemented without seeking approval from Regulatory Authorities or Ethics Committees in the countries where the clinical trial is being conducted.

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

USM and SAE forms are to be submitted to [redacted] or sent by fax to [redacted] (North America) or [redacted] (EMEA, APAC).

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 patient; provide 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 IMP.

15.7.3 Reporting Suspected Unexpected Serious Adverse Reactions

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

- Serious: as defined in Section 15.2 of this protocol.
- Unexpected: AE is not consistent with the Reference Safety Information (found in the IB).
- Suspected Adverse Reaction: relationship to IMP is suspected to be related as defined in Section 15.6 of this protocol.

All SUSARs should be reported to the relevant Regulatory Authority, to EC/IRBs in accordance with the local EC/IRB requirements, and Investigators as per the regulatory requirement and timelines.

15.8 Pregnancy

In a pivotal fertility study in rats, KVD900 was very well tolerated with no findings at up to and including the maximum dose level of 600 mg/kg/day (human equivalent dose [HED] would be 5,800 mg in a 60 kg person). In the pivotal rat and rabbit embryo-fetal studies, dose levels up to and including 300 mg/kg/day KVD900 (HED 2,900 mg in a 60 kg person) were well tolerated and only elicited slight maternal toxicity in terms of lower body weight gain resulting in a slight reduction in fetal weight in the rabbits, with no effect in the rats. There was no effect on embryo-fetal development in either species at this dose level. At the NOAELs in these pivotal fertility and embryo-fetal studies, a large plasma exposure margin was observed compared to exposure following a dose of 600 mg to humans.

A female patient who becomes pregnant while participating in the trial must notify the Investigator immediately. The patient must discontinue treatment with the investigational product but may continue other trial procedures at the discretion of the Investigator. The procedure for discontinuation of a patient will be followed, as described in Section 13.

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

All pregnancies must be reported by the Investigator to the Sponsor or designee within 5 days after becoming aware of the pregnancy. Pregnancies will be reported using the pregnancy reporting form and submitted to [redacted]. The Investigator should make every effort possible to follow-up and document the course and the outcome of all pregnancies and live births up to 1 year of age even if the patient was discontinued from the trial or if the trial has finished.

If a female partner of a male trial patient who has been exposed to the IMP becomes pregnant and consents to having the pregnancy followed, the pregnancy and outcome of pregnancy should be monitored according to the same guidelines as for female patients who become pregnant during the trial.

15.9 Treatment of Overdose

No specific antidote to KVD900 is known and treatment of overdose should be supportive.

16. TRIAL PROCEDURES

This trial will be conducted on an outpatient basis and will comprise in-clinic and televisits. A televisit can be conducted via a telephone call or via an interactive audio/video system. If an in-clinic visit cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the patient from attending in-clinic visits), home health visits will be used to perform these visits, if permitted by the relevant regulatory authority, site's EC/IRB, local regulations, and the patient via informed consent. The home visit will be performed by an appropriately delegated home healthcare service provider. Information captured during a home health visit will mirror that captured in an in-clinic visit. The IMP will be shipped to the patient via a courier service as described in the Pharmacy Manual. If local regulations or the site's local practices do not allow the IMP to be delivered to the patient via courier service, then the patient will need to return to the clinic for the Randomization Visit where IMP will be dispensed.

Informed consent must be obtained for all patients participating in the trial prior to performing any trial-related activities.

Trial procedures are summarized by trial visit in the Schedule of Events (Table 1).

16.1 Screening Period

16.1.1 Screening Visit (In-Clinic or Home Health Visit)

Patients will undergo an in-clinic or home health visit for the Screening Visit. All patients will sign an Informed Consent Form (ICF) and provide assent (if applicable) prior to any trial-related procedures being performed. Consent/assent may be collected through e-consent, if allowed through country and site regulations. Following full discussion of the trial and the signing of the informed consent/assent, a patient number will be assigned (Section 11.1).

The following activities will be performed during the Screening Visit:

- Eligibility assessment evaluating all results of the screening assessment results against the inclusion and exclusion criteria (Section 9).
- HAE diagnostic lab test (or confirmation against documented historical testing results) for patients without genetic confirmation of HAE type I or II.
- Full medical history (Section 14.1), including any relevant previous and concurrent diseases, HAE disease history including the attack history and corresponding treatment for the past 3 months; therapies and supplements taken within the past 4 weeks; and previous participation in interventional clinical trials in the past 4 weeks.
- Demographic information including year of birth; race and ethnicity (if allowed); and sex (Section 14.1).
- Height (m; without shoes) and weight (kg) (Section 14.1).
- Complete physical examination (Section 14.3.1).
- Vital signs (SBP and DBP, PR, and RR). BP and PR recorded after patient has been resting for at least 5 minutes (Section 14.3.2).
- 12-lead ECG after patient has been supine for at least 5 minutes (Section 14.3.3).
- Serum pregnancy test (female patients of childbearing potential).

- Blood and urine samples for clinical laboratory tests (Section 14.3.4).
- Patient eDiary training on the information they will be expected to provide in the eDiary and the use of IMP.

16.2 Randomization Visit (Televisit or In-Clinic)

The Randomization Visit may be a televisit or an in-clinic visit and will occur within 4 weeks of completing the Screening Visit. A televisit can be conducted via a telephone call or via an interactive audio/video system.

The following activities will be performed during the Randomization Visit:

- Eligibility assessment evaluating all results of the screening assessment results against the inclusion and exclusion criteria (Section 9).
- Patient eDiary training.
- Prior medication review.
- Randomize patient in RTSM.
- Dispense or ship the assigned, blinded IMP to patients.

The IMP will be shipped directly to the patient via a courier service or will be dispensed at the trial clinic as required by local regulations or per the site's local practice, as described in the Pharmacy Manual.

16.3 Treatment Period

The Treatment Period will begin when the first HAE eligible attack occurs. Patients will treat 3 separate, eligible HAE attacks with their assigned IMP treatment for that attack. For an HAE attack to be considered eligible for treatment with IMP, the attack must meet the following criteria:

- The attack is not a severe laryngeal attack.
- Patient must be able to identify the start time of the attack.
- At least 48 hours have elapsed since patient has used conventional on-demand treatment or IMP to treat an HAE attack.
- Patient must be able to complete at least the first 4 hours of diary assessments following the first administration of IMP.
- Post-attack televisit has been completed for the previous eligible attack (applicable to eligible attacks 2 and 3 only).

Patients will treat each attack with up to 2 of doses IMP, administered at least 3 hours apart. Eligible attacks should initially be treated with a single administration of IMP. Patients will be encouraged to treat as soon as possible after recognition of the start of the attack.

If needed (as determined by the patient), a second dose of IMP may be administered for each non-laryngeal or laryngeal attack, as follows (see Figure 2 for schematic):

Non-laryngeal attacks

For each eligible HAE attack, a second dose of IMP may be taken:

- after **3** hours if HAE attack symptoms are considered severe enough by the patient to require a second dose of IMP.

After the second dose of IMP, conventional on-demand treatment may be taken:

- after **1** hour if HAE attack symptoms are considered severe enough by the patient to require treatment with conventional treatment.

If symptoms progress to airway involvement, patients may treat with conventional on-demand treatment at any time.

Laryngeal attacks

After the first dose of IMP, conventional on-demand treatment may be taken at any time:

- if HAE attack symptoms worsen or if HAE attack symptoms are considered severe enough by the patient to require immediate treatment.

Patients with safety or tolerability concerns will contact the Investigator or designee as soon as possible or the nearest emergency service as appropriate.

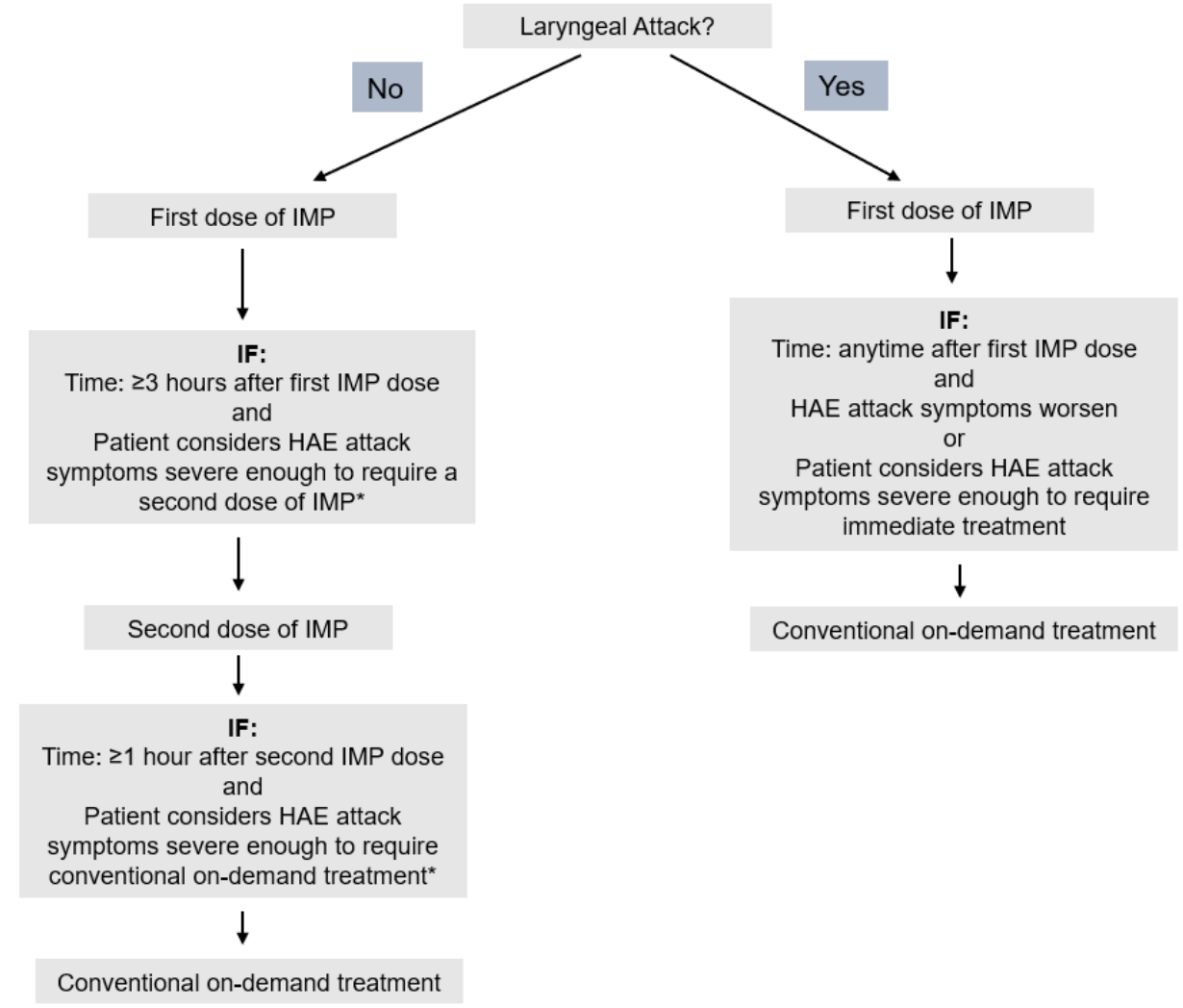


Figure 2: Schematic of Repeat Dosing

16.3.1 First, Second, and Third Eligible HAE Attack (Televisit)

At the time of the first, second, and third HAE attack, the following activities will be performed:

Patient Activities

- Patients will contact the Call Center after the first dose of IMP, prior to a second dose of IMP, and prior to a dose of conventional on-demand treatment.
- Call Center staff will remind patients of the rules for re-dosing and the eDiary assessment requirements and will instruct patients experiencing laryngeal attacks to call their study doctor.

- Patients will complete timed assessments of HAE attack symptoms, including PGI-C, PGI-S, VAS and GA-NRS through 48-hour period following first dose of IMP.

Site Staff Activities

For each of the 3 eligible HAE attacks, a televisit will occur by the next working day after the completion of the patient diary (visit window: +1 week), during which the clinical site staff will perform the following:

- Patient eDiary reviewed with re-training, if necessary.
- Concomitant medication review.
- AEs recorded (Section 15).

16.3.2 Final Visit/Early Termination (In-Clinic or Home Health Visits)

Once 3 separate HAE attacks have been treated with IMP, or upon patient ET, the patient should return to the clinic for the final visit as soon as possible within 1 week of completing all patient diary assessments. Whenever possible this visit should be completed prior to starting any new medication or treatment. At the Final Visit (or ET) the patient will return to the clinic and the following procedures will be conducted:

- Symptom-directed physical examination (Section 14.3.1). In the case of a home health visit, the home healthcare nurse will conduct an abbreviated physical examination, and the Investigator will conduct the symptom-directed physical examination via televisit.
- Vital signs (SBP and DBP, PR, and RR). BP and PR recorded after patient has been resting for at least 5 minutes (Section 14.3.2).
- 12-lead ECG after patient has been supine for at least 5 minutes (Section 14.3.3).
- Blood and urine samples for clinical laboratory tests (Section 14.3.4).
- Serum pregnancy test (female patients of childbearing potential).
- Return unused IMP and IMP packaging (or arrange for return if in-clinic visit is not possible).
- Concomitant medication review.
- AEs recorded (Section 15).

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size Determination

Approximately 114 patients will be randomized into the trial to ensure approximately 84 patients (including approximately 12 adolescents) complete the trial. The trial population will comprise 2 subsets: (1) patients who enter the trial taking only conventional on-demand treatment; and (2) patients who enter the trial on a stable dose and regimen of long-term prophylactic treatment.

1. Based on the population and results from the Phase 2 trial (KVD900-201), a sample size of 66 patients completing the trial would provide 90% power for testing each pairwise comparison (KVD900 versus placebo) at the 2.5% alpha level (2-sided) for the primary endpoint of time to beginning of symptom relief of the HAE attack as defined by PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP administration. This sample size was derived using the assumption that median time to symptom relief of the HAE attack is 1.6 hours in active dose arm and 9 hours in placebo arm from trial KVD900-201. It was assumed that patients begin the trial together and will be followed for the same period of time, 49% of patients in control group and 17% of patients in KVD900 dose group are assumed to be lost-to-follow-up (right-censored).

   There is no commercially available software for sample size calculation based on the Feingold and Gillespie (1996) method. Taking a conservative approach and using simulation-based procedure for power calculations for a parallel group design, the two-sided two-group survival comparison Gehan-Wilcoxon test has approximately 90% power to detect a median time ratio of 5.6 (9/1.6) with a target 2-sided significance level of 2.5% when there are 66 patients in each treatment group.
2. The treatment effect observed in the Phase 2 trial (KVD900-201) is assumed to be representative of the entire KVD900-301 population. However, additional trial populations will be enrolled (e.g. adolescent patients and patients that enter the trial on a stable dose and regimen of long-term prophylactic treatment) where the treatment effect has not been previously characterized. Therefore, a total of 84 patients completing the trial is proposed. This conservative approach increases the likelihood of maintaining at least 90% power in the event that the true treatment effect in the KVD900-301 population is different to that observed in the KVD900-201 trial.

Assuming there is approximately 30% dropout or non-completion rate, consistent with the Phase 2 trial, the oversampling by 30 patients (84 + 30 = 114) is proposed to account for patients that may not complete all treatment periods due to infrequent or ineligible HAE attacks or for patients who discontinue the trial early, for whatever reason.

17.2 Estimands and Intercurrent Events

Table 6: Intercurrent Event Types

Label	Intercurrent Event Type
IcEv1 (Discontinue trial due to any reason)	Discontinuation of trial due to any reason
IcEv2 (Prohibited medications)	Use of prohibited medications that may interfere with outcome (Section 12.3)
IcEv3 (Conventional on-demand treatment)	Use of conventional on-demand treatment that may interfere with outcome (Section 12.1)

Abbreviations: IcEv=intercurrent event

Table 7: Estimands with Rationale for Strategies to Address Intercurrent Events

Estimand Label	Primary Estimand.
Estimand Description	Relative effect of each of the KVD900 dose groups versus placebo in shortening the time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration in adolescent and adult patients with hereditary angioedema type I or II regardless of prohibited medications and as long as conventional on-demand treatment for HAE attacks had not been used and as if patients had not discontinued the trial.
Target Population	Adolescent and adult patients with hereditary angioedema type I or II .
Endpoint	The PGI-C: Time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of the first IMP administration.
Treatment Condition(s)	Initially, a single dose of KVD900 300 mg, 600 mg, or matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), a second dose of IMP may be administered for each attack. Attacks that do not meet eligibility may be treated with conventional on-demand treatment per the patient's usual treatment regimen.
Population-Level Summary	Difference in median time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration.
Intercurrent Event Strategy	
IcEv1 (Discontinue due to any reason)	Hypothetical.
IcEv2 (Prohibited medications)	Treatment policy.
IcEv3 (Conventional on-demand treatment)	Composite.
Rationale for Strategies	The primary focus of this Phase 3 trial is to demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks regardless of the prohibited medication taken as long as conventional on-demand treatment has not been used and as if patient did not discontinue the trial.

Abbreviations: HAE=hereditary angioedema; IcEv=intercurrent event; IMP=investigational medicinal product; PGI-C=Patient Global Impression of Change

17.3 Populations for Analyses

- Safety Set will include all patients who receive at least one dose of trial medication.
- Full Analysis Set (FAS) will include all randomized patients who receive trial medication from at least one period for respective qualifying HAE attack. If one or more patient(s) received incorrect trial medication, data summarized using the FAS will be presented according to the randomized treatment. The FAS population will be the population for confirmatory efficacy analyses.
- Per-protocol Set (PPS) will include all randomized patients who receive trial medication from at least one period for respective qualifying HAE attack, and who do not have major protocol deviations that may affect primary efficacy endpoint.

Subgroup analysis sets

- On-demand Full Analysis Set (on-demand FAS) will include FAS patients who enter the trial taking only conventional on-demand treatment.
- Prophylaxis Full Analysis Set (prophylaxis-FAS) will include FAS patients who enter the trial on a stable dose and regimen of long-term prophylactic treatment.

17.4 General Considerations

Continuous data will be summarized by treatment group using descriptive statistics (number, arithmetic mean, median, standard deviation, 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.

The primary efficacy endpoint confirmatory analysis will have Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests will be 2-sided with an alpha of 0.025. The analysis of the secondary or exploratory endpoints will not have multiplicity adjustments.

There are 3 treatment groups in the trial:

1. 300 mg KVD900
2. 600 mg KVD900
3. Placebo

Two pairwise comparisons will be performed: 300 mg KVD900 versus placebo and 600 mg KVD900 versus placebo.

17.4.1 Multiplicity Adjustment

Fixed sequence closed testing procedure will be followed. In a fixed sequence closed testing procedure the formal inferential testing can proceed to the next step only when statistical significance is declared in the current step. If the testing sequence is stopped, the remaining endpoints in the testing sequence will be considered exploratory. The fixed testing procedure will be employed first on the primary and then on the key secondary endpoints 1 and 2, separately for each dose comparison to placebo.

Primary Endpoint

- PGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration.

Key Secondary Endpoints

- PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration.
- PGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration.

Statistical tests on both the primary and the key secondary endpoints will be at the same significance level alpha (0.025) with a loop-back feature to allow two-way alpha passing. Key secondary endpoint 1 will be tested only if the test on the primary endpoint is statistically significant. Testing within a dose level will be stopped if the test on the primary endpoint could not reject null hypothesis for that KVD900 dose level at significance level of 0.025.

Key secondary endpoint 2 will be tested only if the test on the key secondary endpoint 1 is statistically significant. Testing within a dose level will be stopped if the test on the key secondary endpoint 1 could not reject null hypothesis for that KVD900 dose level at significance level of 0.025.

Significance level 0.025 is Bonferroni adjusted significance level obtained by dividing the original significance level 0.05 by the number of comparisons within endpoint family between each KVD900 dose level and placebo, i.e. the adjusted significance level is 0.025 (0.05 divided by 2). If the primary and key secondary endpoints hypotheses within one of the pairwise comparisons are not all rejected at 0.025 alpha level, but the hypotheses for the other pairwise comparison are all rejected, then the unused alpha from the rejected hypotheses can be directed to loop-back to the unrejected hypotheses, which is then re-tested at the alpha level of 0.05.

17.5 Analysis of Disposition

The number and percentage of patients screened, entering, and completing each trial part will be presented by treatment. Reasons for withdrawal will be summarized.

17.6 Demographics and Baseline Characteristics

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.

17.7 Statistical Analysis of Efficacy Endpoints

17.7.1 Primary Endpoint

Primary Analysis Hypothesis

The null hypothesis is that there is no difference in survival distribution of the time to beginning of symptom relief defined by the PGI-C as at least “a little better” for 2 time points in a row within 12 hours of the first IMP administration (no difference between each dose of KVD900 group versus placebo group) versus the alternative hypothesis that the survival distributions are different (each of the KVD900 dose groups versus placebo).

$$H_0: t_k - t_p = 0,$$

where t_k is the time to “a little better” or higher rating of HAE attack following KVD900 dose treatment and t_p is the time to “a little better” or higher rating of HAE attack following placebo.

$$H_a: t_k - t_p \neq 0.$$

The number of patients with the primary endpoint event will be summarized by frequencies and survival estimates, the summaries will be presented by treatment.

Table 8 gives a summary of analysis methods, strategy for handling missing data, and sensitivity analysis for the primary endpoint.

Table 8: Summary of Statistical Methods and Sensitivity Analyses for Primary Endpoint

Estimand Label	Estimand Description	Main Estimation			Sensitivity/ Supplementary Analysis
		Analysis Set	Imputation/Data/ Censoring Rules	Primary Analysis Model/ Method	
Primary Estimand	Relative effect of each of the KVD900 dose groups versus placebo in shortening the time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration in adolescent and adult patients with hereditary angioedema type I or II regardless of prohibited medications and as if conventional on-demand treatment for HAE attacks had not been used and patients had not discontinued the trial.	FAS	Patients will be treated as right-censored if they do not achieve beginning of symptom relief defined by PGI-C as at least "a little better" (2 time points in a row) within 12 hours of the first IMP administration (plasma KVD900 levels are expected to be low by 12 hours). In the case intercurrent events prevented event "a little better" or higher HAE attack rating occurrence, patients will be censored.	Time to beginning of symptom relief defined by the PGI-C as at least "a little better" for 2 time points in a row within 12 hours of the first IMP administration will be analyzed using Gehan score transformation test proposed by Feingold and Gillespie (1996) (Section 17.7.2)	**Sensitivity Analysis 1**: Perform imputation under informative censoring (Section 17.7.3) and repeat primary analysis. **Sensitivity Analysis 2**: Generalized Wilcoxon test proposed by Feingold and Gillespie (1996) adapted for 3x3 design (Section 17.7.4). **Supplementary Analysis 1**: repeat primary analysis on PPS. **Supplementary Analysis 2**: Time to beginning of symptom relief will be categorized into intervals and the number and percentage of attacks that fall into each category will be presented. **Supplementary Analysis 3**: Perform imputation for patients who took rescue medication after having worsened using a hypothetical strategy, i.e. their time to beginning of symptom relief will be imputed as right-censored at time of rescue medication. Repeat primary analysis.

Abbreviations: FAS=Full Analysis Set; HAE=hereditary angioedema; IMP=investigational medicinal product; PGI-C=Patient Global Impression of Change; PPS=Per-protocol set

17.7.2 Gehan Score Transformation Test

The Gehan Score Transformation test was proposed by Feingold and Gillespie (1996). For this test, applicable to any cross-over design, they propose to transform each observation to a score and then apply the procedures for complete data to the scores: “Scores for censored data are analogous to ranks for complete data, and this score transformation approach is analogous to the rank transformation analysis often used for complete data”. To perform the test, each observation will be transformed to Gehan score. Gehan score for the i^{th} observation is the number of observations in the entire data set clearly smaller than the i^{th} minus the number clearly larger. For uncensored observations, the Gehan score is the number of uncensored observations strictly smaller, minus the number of uncensored observations strictly greater, minus the number of right-censored observations equal or greater. For right-censored observations, the Gehan score is the number of uncensored observations smaller or equal.

Gehan scores will be analyzed using a linear mixed model, including terms for sequence, period and treatment in the model as fixed effects and sequence within patient as a random effect. Least-squares means of treatment effects to show differences between treatments (placebo versus 600 mg versus 300 mg) will be tested at 0.025 level.

17.7.3 Imputation under Informative Censoring

For this first sensitivity analysis, censored observations will be treated as missing data. Nonparametric multiple imputation under informative censoring assumption will be applied to impute censored data. Informative censoring assumes correlation between failure and censoring time (Taylor et al. 2002, O’Connor 2020). Censored or missing outcome values will be imputed from a distribution derived from remaining at risk patients. The first steps of the imputation method will be to identify this distribution, followed by the random selection of the imputed value until new multiple imputed data set is created. The procedure will be independently repeated 50 times creating 50 multiply imputed data sets. The primary analysis will be repeated on each of the 50 multiply imputed data sets and the results will be combined using Rubin’s method. Details on the test implementation will be provided in the Statistical Analysis Plan (SAP).

17.7.4 Gehan’s Generalized Wilcoxon Test

The Gehan’s generalized Wilcoxon test was also proposed by Feingold and Gillespie (1996). The test is a non-parametric test for comparing time-to-event data and is an extension of the Wilcoxon rank sum test in the presence of censoring. The test was designed for trials with two sequences.

This supplementary analysis will explore adapting this test for 3x3 crossover design, by pooling pre-specified sequences and implementing this test as if comparing two treatment groups, the pairwise difference between periods (corresponding to the relevant KVD900 dose versus placebo) in time to at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration using PGI-C will be calculated, separately by sequence. Details on the test implementation will be provided in the SAP.

17.7.5 Key Secondary Endpoints

- PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration.

- PGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration.

HAE attack severity will be assessed on the PGI-S 5-point Likert scale scored as none, mild, moderate, severe, and very severe. A decrease in severity is defined as any change to any less severe level post baseline, than the score reported at baseline.

Key secondary endpoints will be analyzed with the same approach as primary endpoint analysis method (Gehan Score Transformation test, Section 17.7.2). For both key secondary endpoints (Section 7.2.2) the same as for primary endpoint hypotheses (Section 17.7.1) will be tested.

Key secondary endpoints will be tested according to the fixed sequence closed testing procedure (Section 17.4.1).

Key secondary endpoints will be summarized by frequencies and survival estimates; the summaries will be presented by treatment.

17.7.6 Subgroup and Subset Analyses

Subgroup analyses of the primary and key secondary efficacy endpoint will be performed by primary attack location at HAE attack onset, gender, age, prophylactic treatment status, type of HAE, Baseline severity, region, time from onset of attack to the first IMP administration, and number of doses received. Frequencies and survival estimates will be presented for each subgroup. Subgroups by time of attacks may also be investigated.

Analysis of the primary and key secondary efficacy endpoints will be performed on the on-demand FAS and the prophylaxis-FAS.

17.7.7 Other Endpoints

Secondary endpoints listed in Section 7.2.3 are time-to-event endpoints. The time-to-event endpoints will be summarized by frequencies of the events and Kaplan-Meier estimates or survival estimates as appropriate. The summaries will be presented by treatment.

Additional endpoints may be defined in the SAP. The details of the statistical analysis will be provided in the SAP.

17.7.8 Exploratory Endpoint(s)

Baseline- and time-adjusted AUCs of the GA-NRS over time from 0 hour (pre-dose) up to 12 hours and up to 24 hours or up to the last time point prior to the time of conventional on-demand treatment use, whichever occurs first will be derived by linear trapezoidal rule. Details on AUC calculation will be provided in the SAP. AUCs will be summarized descriptively. A statistical comparison of the AUCs between treatments will be performed using a mixed effects analysis of variance with fixed effects of treatment, sequence, and period and patient nested within sequence as a random effect.

Additional endpoints may be defined in the SAP.

17.8 Safety Analyses

Safety analyses will be performed by treatment group using the safety set. Safety endpoints include AE, clinical laboratory assessments, vital signs, ECG findings as described in Sections 14.3 and 15.1.

Adverse events and SAEs recorded during the trial will be summarized by system organ class, preferred term, and treatment. Adverse events and medical history will be coded using the most current version of MedDRA.

Frequencies and percentages of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group.

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

For physical examination, ECG, vital signs, and laboratory variables (measured by the central laboratory), the number and percentage of patients with normal or abnormal results will be presented at each scheduled visit by sequence. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter by sequence.

17.9 Interim Analyses

Not applicable.

18. TRIAL ADMINISTRATION

18.1 Direct Access to Source Data/Documents

The Investigator will allow Sponsor representatives, authorized regulatory authority inspectors, and the EC/IRB to have direct access to all documents pertaining to the trial.

These groups may audit and review source data and will follow local regulations regarding data protection. The Investigator will provide support for these audits.

18.2 Quality Control and Quality Assurance

The Sponsor and Contract Research Organization (CRO) will utilize a system of quality assurance. Within this system, Standard Operating Procedures (SOPs) from the Sponsor and CRO will be followed to ensure the clinical trial is conducted in compliance with regulatory requirements and GCP. Quality control will be applied to each stage of data handling.

18.3 Ethics

18.3.1 Regulatory and Ethical Considerations

The procedures set out in this clinical trial protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP, applicable local regulatory requirements, and the Declaration of Helsinki (World Medical Association, 2013). The clinical trial will also follow national and local legal requirements.

The trial protocol and relevant documents will be approved by EC/IRB and Regulatory Authorities. The Investigator will provide periodic reports, as required, to the EC/IRB and Regulatory Authorities.

18.3.2 Informed Consent/Assent

Informed consent/assent will be obtained from the patient according to the regulatory and legal requirements of the participating country. This may be captured electronically or via paper. The Investigator will not undertake any investigation specifically required for the clinical trial until valid consent/assent has been obtained.

18.3.3 Patient Confidentiality

The anonymity of participating patients must be maintained. Patients will be specified on trial documents by their patient ID, not by name. Documents that identify the patient (e.g. informed consent document) must be maintained in confidence by the Investigator per GCP and local regulations.

The Investigator agrees not to use or disclose protected health information other than as permitted or required by patient authorization or as required by law.

18.4 Data Handling and Record Keeping

18.4.1 Source Documents

All source documents from which eCRF entries are derived should be placed in the patient's trial records. Source documents may include laboratory assessments, trial specific examinations, and any other documents that support the data collected in the eCRF. The Investigator will ensure the accuracy, completeness, and timeliness of the data. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

18.4.2 Trial Monitoring

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

The Investigator will maintain adequate and accurate records of data pertinent to the clinical trial for each trial patient. Frequent communication between the trial site and the Sponsor (or designee) is essential to ensure that the trial is monitored adequately.

All aspects of the trial will be carefully monitored with respect to GCP, Sponsor and CRO SOPs, and the trial specific Monitoring Plan to ensure compliance with applicable government regulations. The Monitor(s) will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the trial with the Investigator.

18.4.3 Database Management

All data generated by the site personnel will be captured electronically at each trial site using eCRFs. A complete audit trail will be maintained of all data changes.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to trial sites. Applicable site personnel will receive training on the eCRF. Edit checks and manual review will be used to identify any errors or inconsistencies in the data.

18.4.4 Retention of Trial Records

Essential documents, including all trial records, should be retained according to ICH guidelines. These documents should be retained for a longer period if required by the applicable local regulations.

If the responsible Investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

18.5 Financing and Insurance

18.5.1 Financial Disclosure

All Investigators and required trial personnel will complete a financial disclosure statement.

18.5.2 Trial Insurance

Clinical trial insurance will be maintained per local regulations.

18.6 Publication Policy

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. The rights and obligations of Investigators and the Sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this trial will be addressed specifically in the Clinical Trial Agreement for the trial.

18.7 Trial Master File

A Trial Master File (TMF) will be maintained by the Sponsor (or designee). Documents and other materials that pertain to the conduct of the trial, quality of the data, and compliance with GCP will be collected in the TMF.

18.8 Premature Trial Closure

The Sponsor reserves the right to prematurely terminate or halt the trial either at a particular site or at all trial sites at any time after appropriate discussion with the Sponsor and Investigator(s). If the trial is halted or terminated for safety reasons, then all Investigators and the relevant Regulatory Agencies will be notified per local regulations. The Investigator at each trial site will advise their EC/IRB.

18.9 Selection of Coordinating Investigator

A coordinating (principal) investigator will be appointed as a signatory on the clinical study report in accordance with EMEA guidance and Sponsor requirements.

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