CLINICAL TRIAL PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of Three Dose Levels of KVD824, an Oral Plasma Kallikrein Inhibitor, for Long-Term Prophylactic Treatment of Hereditary Angioedema Type I or II

Protocol Number:	KVD824-201
Protocol Name	KOMPLETE
Compound:	KVD824 (300 mg Modified-Release Tablet)
Trial Phase:	2
Sponsor:	KalVista Pharmaceuticals, Ltd. Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom
IND Number:	152196
EudraCT Number:	2021-000136-59
Date of Protocol:	31 March 2022, Version 5.0 05 May 2021, Version 4.0 29 March 2021, Version 3.0 16 February 2021, Version 2.0 27 January 2021, Version 1.0
Compliance	This trial will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on Harmonization), 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 2 Trial to Evaluate the Efficacy and Safety of Three Dose Levels of KVD824, an Oral Plasma Kallikrein Inhibitor, for Long-Term Prophylactic Treatment of 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).

DocuSigned by:
Paul Audhya MD
Signer Name: Paul Audhya MD
Signing Reason: I approve this document
Signing Time: April 1, 2022 | 17:43:46 BST
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Paul Audhya, MD, MBA
Chief Medical Officer
KalVista Pharmaceuticals, Ltd.

DocuSigned by:
Signer Name: Matthew Iverson
Signing Reason: I approve this document
Signing Time: April 1, 2022 | 15:35:49 BST
6AE67D8793664F1B84C94CF1B098818B

Matthew Iverson, MPH
Vice President, Clinical
KalVista Pharmaceuticals, Ltd.

2. DECLARATION OF THE INVESTIGATOR

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of Three Dose Levels of KVD824, an Oral Plasma Kallikrein Inhibitor, for Long-Term Prophylactic Treatment of 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 subjects.

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)

CHANGES FROM PROTOCOL VERSION 4.0 TO VERSION 5.0 AND RATIONALE FOR THESE CHANGES

Changes introduced into Version 5.0 of the protocol are as follows:

- Clarified that serious adverse events will be collected beginning at the time of informed consent through the Week 12/Early Termination Visit.
- Extended the timing in which subjects may be retested if Screening functional C1-esterase inhibitor and C4 levels are below the normal range from occurring during the Screening Period to occurring prior to randomization, and clarified that diagnostic testing results may be obtained from documented historical testing.
- Changed the timing of allowable last dose of attenuated androgens prior to study entry from prior to randomization to prior to first dose of investigational medicinal product (IMP).
- Added a safety draw for clinical chemistry and liver enzymes at Week 4.
- Added liver-related adverse event that meets Hy's Law in more than 1 subject as a trial stopping criterion.
- Removed IMP temperature storage ranges from the protocol and clarified that IMP is to be stored at room temperature as labeled.
- Added procedural details for Investigators if unblinding a subject is needed.

Minor typographical corrections and editorial changes are not described above.

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3. SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of Three Dose Levels of KVD824, an Oral Plasma Kallikrein Inhibitor, for Long-Term Prophylactic Treatment of Hereditary Angioedema Type I or II
Trial No	KVD824-201
Protocol Name	KOMPLETE
Phase	2
Trial Centers	HAE treatment centers worldwide
Objectives	**Primary Objective** • To demonstrate the clinical efficacy of prophylactic treatment with KVD824 compared with placebo in preventing hereditary angioedema (HAE) attacks. **Secondary Objectives** • To further characterize the clinical efficacy of KVD824. • To investigate the safety and tolerability of KVD824.
Trial Design	KOMPLETE is a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 2 clinical trial to investigate the efficacy and safety of prophylactic treatment with three dose levels of KVD824 in subjects with HAE Type I or II. Subjects will be recruited through HAE treatment centers worldwide. This trial will be conducted on an outpatient basis and will comprise in-clinic visits or home health visits when in-clinic visits cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the subject from attending the in-clinic visits). **Screening Period** Screening Visit The Screening Period includes the Screening Visit and Run-in Period. All subjects will sign an Informed Consent Form prior to any trial-related procedures being performed. Consent may be collected through a remote e-consenting solution if allowed through country and site regulations. Subjects will be 18 years of age or older at the time of screening and will have a diagnosis of HAE Type I or II. During the visit a physical exam, 12-lead electrocardiogram (ECG), laboratory tests, and other assessments as outlined in the Schedule of Events (Table 1) will also be performed. Site personnel will train subjects on the requirements for reporting attacks and the information subjects will be expected to provide in the electronic diary (eDiary) provided by the study sponsor. The subject will confirm understanding of what is required for reporting attacks.

	Run-in Period Screened subjects will enter a Run-in Period of up to 8 weeks in duration. The start of the Run-in Period is determined by the type of HAE therapy being used by the subject at the time of Screening, as follows: • **Use of On-demand Therapy Only for Treatment of HAE Attacks:** Subjects using only on-demand therapy will enter the Run-in Period upon completion of Screening Visit eDiary assessments. • **Use of Prophylaxis Therapy for Treatment of HAE Attacks:** Subjects using any prophylaxis therapy will enter the Run-in Period following the first Investigator-confirmed HAE attack after discontinuation of all prophylactic therapy. This attack does not count towards the total attacks required to meet the run-in eligibility criteria. Subjects must enter the Run-in Period within 8 weeks of completion of Screening Visit eDiary assessments. During the Run-in Period, all subjects must meet one of the following eligibility criteria: • Two Investigator-confirmed attacks in the first 4-week period. • Three Investigator-confirmed attacks in ≤8 weeks. Once the above Run-In Period criterion is met subjects may proceed to the Randomization Visit. Subjects who do not meet the run-in criterion will be ineligible to randomize and will not be allowed to re-screen. **Randomization Visit** Subjects will complete a Randomization Visit within approximately 10 days of completing the Run-in Period. Subjects will be randomized 1:1:1:1 to receive one of the following treatments to be taken twice daily: • 300 mg (1 x 300 mg tablet) KVD824 • 600 mg (2 x 300 mg tablets) KVD824 • 900 mg (3 x 300 mg tablets) KVD824 • Matching placebo It will be ensured that a balanced number of subjects assigned to placebo receive either 1, 2, or 3 tablets. Arrangements will be made to dispense to the subject blinded investigational medicinal product (IMP) for twice daily oral self-administration for 12 weeks. The IMP will be shipped directly to subjects via a courier service or will be dispensed at the study clinic as required by local regulations or per the site's local practice. Randomization will be stratified by the number of Investigator-confirmed HAE attacks during the Run-In Period (i.e. ≤3 attacks/4 weeks or >3 attacks/4 weeks). A symptom-directed physical exam, 12-lead ECG, laboratory tests and other assessments as outlined in the Schedule of Events (Table 1) will also be performed during the visit. **Treatment Period** The Treatment Period is 12 weeks in duration and starts with the first dose of IMP. Subjects will be instructed to take their first dose with their next morning meal after receipt of the IMP. During the Treatment Period, subjects will self-administer IMP twice daily (either 300, 600, or 900 mg KVD824 or matching placebo) approximately 12 hours

	apart with their morning and evening meals in accordance with their randomized assignment. Both the Investigator and subject will be blinded to the assigned treatment, but not to the number of tablets assigned (1, 2 or 3).
	
	Use of the following treatments is not permitted during the trial:
	
	• Long or short-term prophylaxis for HAE including:
	  ○ C1-esterase inhibitor (C1-INH) for prophylaxis (e.g. Haegarda, Cinryze, Berinert, Ruconest)
	  ○ Lanadelumab
	  ○ Attenuated androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone)
	  ○ Anti-fibrinolytics (e.g. tranexamic acid)
	  ○ Berotralstat
	  ○ Other investigational therapies for HAE prophylaxis (e.g. garadacimab, PKK-LRx, PHVS416)
	• Angiotensin-converting enzyme (ACE) inhibitors
	• Estrogen-containing medications with systemic absorption including:
	  ○ oral contraceptives including ethinylestradiol or hormonal replacement therapy
	• Strong CYP3A4 inhibitors and inducers
	• Narrow therapeutic index drugs metabolized by CYP3A4 or CYP2C9, or transported by OAT1, OCT2, and OATP1B1, as determined by the Investigator, are also prohibited throughout the trial.
	
	Treatment of HAE attacks during the trial, including the Run-in Period, should be managed per the Investigator's conventional care of their subjects, including use of on-demand therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an on-demand therapy but not as a long or short-term prophylaxis. Administration of the investigational product and trial procedures will continue without alteration to the protocol-specified schedule even if the subject requires an on-demand treatment for an HAE attack during the trial.
	
	During the trial, subjects will be instructed to record details of each HAE attack into an eDiary. Should a subject become incapacitated during an attack and unable to record details, this information can be recorded once the incapacitation has resolved. The subject will record the start and stop date/time of each attack, location(s), symptom(s) including prodromal, impact on activity, use of conventional treatment of each attack, and severity.
	
	As soon as possible following the completion of each attack and within no more than 5 working days, contact will be made between the site staff and the subject to confirm, clarify, and correct any recorded eDiary data. Site staff who collect the HAE attack information from the subject must be designated and qualified to perform this task. Additionally, the designated site staff will ask questions about each attack to assist the Investigator (or qualified designee) with their confirmation of each attack.

	The Investigator (or qualified designee) will assess whether the reported attack was caused by HAE. To be classified as an Investigator-confirmed HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations: • Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region. • Abdominal angioedema: abdominal pain with or without abdominal distension, nausea, vomiting, or diarrhea. • Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx. Despite the presence of these symptoms, the Investigator may determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g. urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g. the subject's abdominal symptoms are attributable to a viral gastroenteritis). To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms. The collection, reporting, and assessment of attacks in this trial will be done in accordance with KalVista's HAE Attack Document (K-HAD). Site personnel will be trained on the K-HAD prior to screening subjects at their site. The Investigator (or qualified designee) will rate the severity of each attack. During the Treatment Period, subjects will complete an in-clinic or home health visit at Week 2, Week 4, Week 6, and Week 12/Early Termination (ET). A 12-lead ECG, laboratory tests, and other assessments as outlined in the Schedule of Events (Table 1) will be performed during the in-clinic or home health visit. Visits should occur within 3 days of Week 2, 4, and 6. The Week 12/ET Visit should occur within 7 days after the final dose of IMP. Subjects will also complete quality of life assessments at the Screening Visit, 4 and 8 weeks after the start of dosing, and at the final dose as described in the Schedule of Events (Table 1). The Treatment Satisfaction Questionnaire for Medication (TSQM) will be completed with the final dose.
Investigational Medicinal Products	KVD824 (300 mg) modified-release tablet. Placebo to KVD824 tablet. No IMP dose modifications are allowed in this trial. Tablets must be swallowed whole; tablets are not to be crushed or modified in any way. Tablets should be taken approximately 12 hours apart with the morning and evening meal.
Number of Subjects	Approximately 48 subjects will be randomized into the trial.
Population	The trial population will include male and female subjects 18 years of age and older with a confirmed diagnosis of HAE Type I or II.

	Inclusion Criteria 1) Male or female subjects 18 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 (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND EITHER b) Diagnostic testing results obtained prior to randomization that confirm HAE Type I or II: C1-INH functional level <40% of the normal level. Subjects 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. Subjects 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 c) Documented genetic results that confirm known mutations for HAE Type I or II. 3) Subject has access to and ability to use conventional treatment for HAE attacks. 4) Subject is willing to cease any current medications being taken for HAE prophylaxis and Investigator determines that doing so would not place the subject at any undue safety risk. 5) Subject's last dose of attenuated androgens was at least 28 days prior to first dose of IMP. 6) During the Run-in Period subject meets one of the following criteria: a) Two Investigator-confirmed attacks in the first 4-week period. b) Three Investigator-confirmed attacks in ≤8 weeks. 7) Subjects who are fertile and heterosexually active must adhere to contraception requirements throughout the trial as follows: a) Female subjects must agree to use at least one highly effective contraception method from the Screening Visit until the end of the trial. Highly effective methods of contraception include: i) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable (hormonal contraception that contains estrogen including ethinylestradiol is excluded per Exclusion 4). ii) Intrauterine device (IUD). iii) Intrauterine hormone–releasing system (IUS). iv) Bilateral tubal occlusion. v) Vasectomized partner (provided that the partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of surgical success). b) Male subjects with a female partner of childbearing potential must agree to use condoms for the entire Treatment Period AND for 90 days following the final dose of IMP. Female partners are encouraged to use contraception as outlined in Inclusion 7a) from the Screening Visit until the end of the trial. Hormonal contraception that contains estrogen including ethinylestradiol is acceptable for the female partner. 8) Subjects who are not fertile or not sexually active, as defined below, do not require contraception. a) Subjects 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 subject. b) Male subjects who are surgically sterile (e.g. vasectomized with medical assessment of surgical success). c) Female subjects who are surgically sterile (e.g. status post hysterectomy,

	bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months. 9) Subjects must be able to swallow trial tablets whole. 10) Subjects assessed by the Investigator must be able to appropriately receive and store IMP, and be able to read, understand, and complete the eDiary. 11) Investigator believes that the subject is willing and able to adhere to all protocol requirements. 12) Subject provides signed informed consent and is willing and capable of complying with trial requirements and procedures. **Exclusion Criteria** 1) Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH (previously known as HAE Type III), idiopathic angioedema, or angioedema associated with urticaria. 2) A clinically significant history of poor response to C1-INH therapy or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. 3) Use of 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) after the Screening Visit or within 7 days prior to randomization. 5) Use of narrow therapeutic index drugs metabolized by CYP3A4 or CYP2C9 or transported by OAT1, OCT2, and OATP1B1, starting at screening, as determined by the Investigator. 6) Use of strong CYP3A4 inhibitors and inducers during participation in the trial, starting at the Screening Visit. 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. 7) Inadequate organ function, including but not limited to; a) Alanine aminotransferase (ALT) > 2x 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. f) Estimated glomerular filtration rate (eGFR) <60 mL/min. 8) Any clinically significant comorbidity or systemic dysfunction that in the opinion of the Investigator would jeopardize the safety of the subject by participating in the trial. 9) History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator. 10) Known hypersensitivity to KVD824 or placebo or to any of the excipients. 11) Any prior use of any gene therapy treatment for HAE. 12) Participation in any interventional investigational clinical trial, 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 subject.

Assessments	**Efficacy Variables**
	• Number (count) of Investigator-confirmed HAE attacks
	• Confirmation of attack by Investigator
	• Assessment of severity by the investigator (or qualified designee)
	• HAE attack descriptions using an eDiary, including:
	  ○ Start and stop date/time of each attack
	  ○ Location(s) of each attack
	  ○ Symptom(s) including prodromal
	  ○ Impact on activity
	  ○ Use of conventional treatment of each attack
	  ○ Subject assessment of severity
	• Quality of Life
	  ○ Angioedema Control Test (AECT)
	  ○ Angioedema Quality of Life Questionnaire (AE-QoL)
	  ○ TSQM
	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** • Rate of Investigator-confirmed HAE attacks during the Treatment Period. **Secondary Endpoints** • Proportion of subjects without Investigator-confirmed HAE attacks during the Treatment Period. • Rate of Investigator-confirmed HAE attacks that require conventional treatment during the Treatment Period. • AE-QoL total score and domain scores during the Treatment Period. • AECT score and domain scores during the Treatment Period. • Proportion of subjects with an AECT score ≥12 at the end of the Treatment Period. **Exploratory Endpoints** • Rate of Investigator-confirmed HAE attacks during the Treatment Period, by severity. • Rate of conventional treatment used during the Treatment Period. • TSQM total scores at the end of the Treatment Period.
General Statistical Methods and Types of Analyses	The statistical analysis plan (SAP) and associated templates for tables, listing and figures will be developed in a separate document that will provide a technical and detailed elaboration of the principal features stated in the protocol and will be developed and finalized prior to trial unblinding. Summary tables, figure and listings will be created using Version 9.4 (or later) of the SAS® software for Microsoft Windows (SAS Institute, Inc., Cary, North Carolina). Qualitative data will be analyzed by number of observed values, and number and percentage of subjects per category.

	Quantitative data will be analyzed by number of observed values, mean and standard deviation (SD), median, first and third quartiles, minimum, and maximum. All statistical tests will be 2-sided with an alpha of 0.05. The primary efficacy endpoint analysis will have Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests will be 2-sided with an alpha of 0.0167. The analysis of the secondary or exploratory endpoints will not have multiplicity adjustments. The primary endpoint will be analyzed by negative binomial regression with randomization stratification factor of baseline attack rate per 4 weeks during the Run-In Period as a fixed covariate and treatment as a fixed factor and the logarithm of time each subject was observed “while on treatment” used as an offset variable in the model. This model will be used to estimate rate of HAE attacks while on treatment and rate ratio of HAE attacks (each of the KVD824 dose groups versus placebo) with 95% confidence interval and 2-sided p-value.

Table 1: Schedule of Events

	Screening Period[a]		**Randomization Visit**	**Treatment Period[b]**			
Visit	Screening Visit	Run-In Period (up to 8 weeks prior to Randomization)		Week 2	Week 4	Week 6	Week 12/ET
In-clinic or Home Health Visit[c]	X		X	X		X	X
Informed Consent[d]	X						
Eligibility Assessment	X		X				
HAE Diagnostic Lab Test[e]	X						
Medical History[f]	X						
Demographics[g]	X						
Physical Examination[h]	X		X				X
Vital Signs[i]	X		X	X		X	X
12-lead ECG[j]	X		X	X		X	X
Safety Laboratory[k]	X		X	X	X	X	X
Pregnancy Test[l]	X		X	X		X	X
Subject eDiary Training	X						
Randomize to Treatment (prior to or during Randomization Visit)			X				
Subject eDiary Re-training (if necessary)			X	X		X	
IMP Dispensing/ Accountability/Return[m]			X	X		X	X
IMP Dosing				BID dosing for up to 12 weeks			
HAE Attack Site Follow-up[n]		◄———	———	———	———	———	———►

Table 1: Schedule of Events

	Screening Period[a]		Randomization Visit	Treatment Period[b]			
Visit	Screening Visit	Run-In Period (up to 8 weeks prior to Randomization)		Week 2	Week 4	Week 6	Week 12/ET
AE-QOL and AECT Questionnaires[o]	X			◄	———	———	►
TSQM							X
Prior and Concomitant Medication Review	◄	———	———	———	———	———	►
Adverse Event Review[p]	◄	———	———	———	———	———	►

Abbreviations: AE-QOL=Angioedema Quality of Life Questionnaire; AECT=Angioedema Control Test; C1-INH=C1-esterase inhibitor; EC = Ethics Committee; ECG=electrocardiogram; eDiary=electronic diary; ET=Early Termination; HAE=hereditary angioedema; IMP=investigational medicinal product; IRB = Institutional Review Board; TSQM=Treatment Satisfaction Questionnaire for Medication.

[a] Procedures for the Screening Visit may take place on different days; however, all procedures should be completed within 4 weeks of starting the visit. For prophylactic subjects, the Run-in Period must start within 8 weeks from completion of Screening Visit eDiary assessments.

[b] The start of the Treatment Period begins with the first dose of IMP with the morning meal after the IMP is received; visits for Week 2, Week 4 (lab draw), and Week 6 should occur within ±3 days. Week 12/ET should occur within 7 days after the last dose of IMP.

[c] If a subject cannot attend a trial in-clinic visit (scheduled or unscheduled), a visit at the subject's home is permitted to occur, if permitted by the relevant regulatory authority, site's EC/IRB, local regulations, and the subject 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 during an in-clinic visit. The home health visits will only occur in the event of a pandemic or other reason that prevents the subject from attending the in-clinic visits.

[d] Consent may be collected through a e-consenting solution if allowed through country and site regulations.

[e] Diagnostic testing must be available for subjects without genetic confirmation of HAE Type I or II.

[f] Medical history includes any relevant previous and concurrent diseases, HAE disease history; therapies and supplements taken within the past 4 weeks; and previous participation in interventional clinical studies in the past 4 weeks.

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

[h] 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.

[i] Vital signs include pulse rate, respiratory rate, and systolic and diastolic blood pressure after subject has been resting for at least 5 minutes.

[j] ECG to be recorded after subject has rested supine for at least 5 minutes.

[k] Laboratory assessments performed by a central laboratory; repeat laboratory assessments may be performed. At the Week 4 visit, a safety lab sample will be drawn to assess clinical chemistry and liver enzymes. This sample can be obtained at a brief in-clinic or site lab visit or can be obtained by a Home Health service provider.

[l] Serum pregnancy test will be performed on females of childbearing potential.

[m] During the Randomization visit, arrangements will be made to dispense the assigned IMP. The IMP will be shipped directly to the subject via a courier service or dispensed at the study clinic as required by local requirements or per the site's local practice, as described in the pharmacy manual. IMP accountability will be performed at the Week 2, 6, and 12/ET visits. Drug accountability will be reviewed at each in-clinic or home health visit (via review of unused IMP), and re-training will occur, if necessary. All unused IMP will be returned at the in-clinic Week 12/ET Visit. If the Week 12/ET Visit is performed by Home Health, arrangements will be made to return any unused IMP via courier.

[n] As soon as possible following the completion of each attack and within no more than 5 working days, contact will be made between the site staff and the subject to confirm, clarify, and correct any recorded eDiary data. Site staff who collect the HAE attack information from the subject must be designated and qualified to perform this task. Additionally, the designated site staff will ask questions about each attack to assist the Investigator (or qualified designee) with their confirmation of each attack. The Investigator (or qualified designee) will rate the severity of each attack.

[o] AE-QOL and AECT Questionnaires will be collected in the eDiary at the Screening Visit, 4 and 8 weeks post initial dose, and with the last dose of IMP.

[p] Adverse events recorded from the first dose of KVD824 or placebo up to and including the Week 12/ET Visit. Serious AEs recorded from the time of signing the informed consent up to and including the Week 12/ET Visit.

4. KEY CONTACT LIST

Sponsor	KalVista Pharmaceuticals, Ltd. Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom Matthew Iverson, MPH Vice President, Clinical Phone: +1 (801) 201-2852 Email: matthew.iverson@kalvista.com
Sponsor Medical Expert	Paul Audhya, MD, MBA Chief Medical Officer Phone: +1 (919) 986-0360 Email: paul.audhya @kalvista.com
Contract Research Organization	PPD Development, L.P. 929 North Front Street, Wilmington, NC 28401 USA
Central Laboratory	PPD Laboratories US 2 Tesseneer Drive Highland Heights, KY 41067 USA
Medical Monitor	Branislav Gvozdenovic, MD, PhD PPD Serbia, Belgrade Phone: North America: 1-888-483-7729 EMEA, APAC: + 44 1223 374 240
Pharmacovigilance for SAE Reporting	Arriello Ireland Limited SAE Reporting Email: kalvista.safety@arriello.com SAE Reporting Fax #: North America: +1 888 215 1304; EMEA, APAC: +420 296 181 216
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
AECT	Angioedema Control Test
AE-QoL	Angioedema Quality of Life
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BID	twice daily dosing
BMI	body mass index
C1-INH	C1-esterase inhibitor
CRO	Contract Research Organization
CSR	clinical study report
DBP	diastolic blood pressure
eCRF	electronic case report form
eDiary	electronic diary
EC	Ethics Committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ET	early termination
F	fraction of non-missing data
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HAE	hereditary angioedema
HbA1c	glycosylated hemoglobin
HDPE	High Density Polyethylene

HCG	Human chorionic gonadotropin
HR	heart rate
IB	Investigator's Brochure
IcEV	intercurrent event
ICH	International Council on Harmonization
IMP	investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone–releasing system
K-HAD	KalVista's HAE Attack Document
kg	kilogram(s)
LOE	lack of efficacy
m	meter(s)
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
mL	milliliter(s)
ms	millisecond(s)
MNAR	missing not at random
$NA_{complete}$	complete number of HAE attacks
$NA_{imputed}$	missing number of HAE attacks
$NA_{observed}$	observed number of HAE attacks
QoL	quality-of-life
pH	potential hydrogen
PR	pulse rate

QTcF	Fridericia correction of QTc
RBC	red blood cell
RR	respiratory rate
RTSM	Randomization and Trial Supply Management System
s	second(s)
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TDD	total daily dose
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal

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 (Gosswein 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 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.

KVD824 is a potent and selective small-molecule inhibitor of plasma kallikrein, a major effector in HAE attacks. Orally administered KVD824 achieves sustained and dose-dependent blockade of plasma kallikrein activity. Inhibition of kallikrein is maintained under fed and fasted conditions. KVD824 further protects high molecular weight kininogen from cleavage, thereby blocking the generation of bradykinin. Refer to the Investigator's Brochure (IB) for further detail on KVD824.

6.3 Benefit/Risk

KVD824 was evaluated in two Phase 1 studies in adult healthy volunteers. Pharmacodynamic evaluations of KVD824 have demonstrated that KVD824 inhibits plasma kallikrein activity *ex-vivo* at levels exceeding equivalent concentrations for berotralstat, a currently approved, once daily, oral plasma kallikrein inhibitor indicated for the prevention of HAE attacks. KVD824 achieved adequate plasma concentrations with sustained plasma kallikrein suppression over a 12- to 14-hour time interval. These data support further investigation of KVD824 as an orally administered treatment with adequate plasma kallikrein suppression to potentially prevent or reduce the occurrence of HAE attacks.

Preclinical investigations, including *in-vitro* and *in-vivo* safety pharmacology studies and animal studies in mice, rats, and non-human primates support KVD824 administration in humans. The doses of modified-release KVD824 to be given in this trial were well tolerated in a previous clinical trial comprising 16 subjects who received single doses of KVD824 up to 900 mg and 21 subjects who received at least 600 mg twice a day for 14 days (Study KVD824-102). All adverse events observed in these studies were of mild and of short duration. No Grade 3 (severe) or serious adverse events (SAE) were reported.

Subjects participating in this study will have access to conventional on-demand therapy to treat HAE attacks. Subjects will be instructed to contact the dedicated trial physician or qualified designee in case of any safety concerns. In the case of hypersensitivity, subjects are expected to contact the dedicated trial physician or qualified designee or contact the nearest emergency service. The site staff will contact the subject after HAE attacks to complete trial assessments.

6.3.1 Impact of COVID-19 on Benefit-Risk Assessment

Significant suppression of plasma kallikrein levels 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 with lanadelumab in subjects with HAE is known to increase susceptibility to viral infections or lead to increased infections in general. Also, epidemiological studies among subjects with HAE have not shown increased risks of infections (Zanichelli et al. 2015). At present plasma kallikrein inhibition with KVD824 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 KVD824 and COVID-19 vaccines. Subjects 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.

7. OBJECTIVES AND ENDPOINTS

7.1 Objectives

7.1.1 Primary

The primary objective of this trial is to demonstrate the clinical efficacy of prophylactic treatment with KVD824 compared with placebo in preventing hereditary angioedema (HAE) attacks.

7.1.2 Secondary

Secondary objectives of this trial are:

- To further characterize the clinical efficacy of KVD824.
- To investigate the safety and tolerability of KVD824.

7.2 Endpoints

7.2.1 Primary endpoint

The primary endpoint of this trial is the rate of Investigator-confirmed HAE attacks during the Treatment Period.

7.2.2 Secondary endpoints

Secondary endpoints of this trial are:

- Proportion of subjects without Investigator-confirmed HAE attacks during the Treatment Period.
- Rate of Investigator-confirmed HAE attacks that require conventional treatment during the Treatment Period.
- Angioedema Quality of Life Questionnaire (AE-QoL) total score and domain scores during the Treatment Period.
- Angioedema Control Test (AECT) score and domain scores during the Treatment Period.
- Proportion of subjects with an AECT score ≥12 at the end of the Treatment Period.

7.2.3 Exploratory endpoints

Exploratory endpoints of this trial are:

- Rate of Investigator-confirmed HAE attacks during the Treatment Period, by severity.
- Rate of conventional treatment used during the Treatment Period.
- Treatment Satisfaction Questionnaire for Medication (TSQM) total scores at the end of the Treatment Period.

7.3 Estimands

Table 2: Primary Objective and Estimand

Objective Description	Estimand Description (Including Endpoint)
To demonstrate the clinical efficacy of prophylactic treatment with KVD824 compared with placebo in preventing hereditary angioedema (HAE) attacks.	Rate of Investigator-confirmed HAE attacks during the Treatment Period. Rate ratio of Investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo) in subjects with a confirmed diagnosis of HAE Type I or II who have at least 1.5 attacks per 4 weeks while off prophylactic treatment. Number of attacks will be measured 'while on treatment' over up to 12 weeks or until their treatment stops or changes (expressed as number of attacks on treatment). Subjects may receive on-demand conventional care for HAE attacks but receipt of additional treatments as a prophylactic would constitute a change and the end of the period considered 'while on treatment.'

8. TRIAL DESIGN

8.1 Overall Design

KOMPLETE is a multicenter, randomized, double-blind, placebo-controlled, phase 2 clinical trial to investigate the efficacy and safety of prophylactic treatment with three dose levels of KVD824 in subjects with HAE Type I or II. Subjects will be recruited through HAE treatment centers worldwide. This trial will be conducted on an outpatient basis and will comprise in-clinic visits. If in-clinic visits cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the subject from attending the in-clinic visits), 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 subject 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.

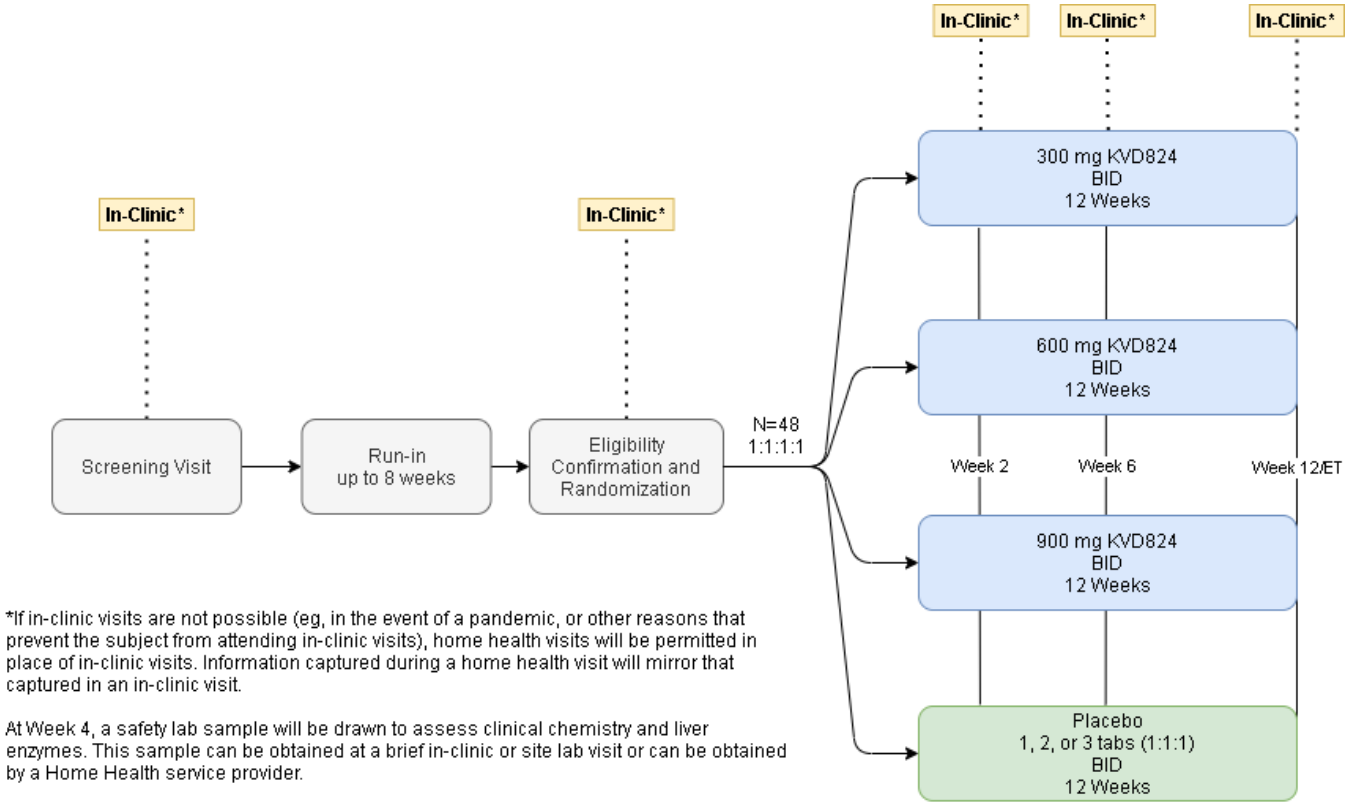

Figure 1: Trial Diagram

8.2 Scientific Rationale for Trial Design

This phase 2 trial is the first clinical investigation of the potential efficacy of KVD824 in the prophylactic treatment of attacks of HAE. The randomized, placebo-controlled parallel group trial design is a standard approach for differentiation between the efficacy and safety profiles of an active and placebo treatments when administered to subjects with HAE Type I or II.

The trial population is representative of the likely target population for the product. The sample size of approximately 48 randomized subjects is required to conclusively evaluate a clinically relevant treatment effect. A trial duration of 12 weeks is adequate to assess the primary and secondary objectives of the trial and other HAE prophylaxis trials.

The twice daily oral dose levels selected for the current clinical trial of KVD824 (300, 600, and 900 mg) are supported by animal toxicology data and were shown in phase 1 trials (of maximum 14-day duration) to be well tolerated and to result in potentially beneficial *ex-vivo* pharmacodynamic effects.

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

A twice daily dose of KVD824 (300, 600, and 900 mg) is supported by the ex-vivo pharmacodynamic bioactivity, pharmacokinetic, safety, and efficacy of KVD824 from previous clinical trials and nonclinical studies that found KVD824 to be well tolerated and to result in potentially beneficial pharmacodynamic effects.

8.4 End of Trial Definition

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

9. TRIAL POPULATION

HAE treatment centers worldwide will randomize approximately 48 subjects into the trial.

9.1 Inclusion Criteria

1) Male or female subjects 18 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 (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND EITHER
   b) Diagnostic testing results obtained prior to randomization that confirm HAE Type I or II: C1-INH functional level <40% of the normal level. Subjects 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. Subjects 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
   c) Documented genetic results that confirm known mutations for HAE Type I or II.
3) Subject has access to and ability to use conventional treatment for HAE attacks.
4) Subject is willing to cease any current medications being taken for HAE prophylaxis and Investigator determines that doing so would not place the subject at any undue safety risk.
5) Subject's last dose of attenuated androgens was at least 28 days prior to first dose of IMP.
6) During the Run-in Period subject meets one of the following criteria:
   a) Two Investigator-confirmed attacks in the first 4-week period.
   b) Three Investigator-confirmed attacks in ≤8 weeks.
7) Subjects who are fertile and heterosexually active must adhere to contraception requirements throughout the trial as follows:
   a) Female subjects must agree to use at least one highly effective contraception method from the Screening Visit until the end of the trial. Highly effective methods of contraception include:
      i) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral/injectable/implantable (hormonal contraception that contains estrogen including ethinylestradiol is excluded per Exclusion 4).
      ii) Intrauterine device (IUD).
      iii) Intrauterine hormone–releasing system (IUS).
      iv) Bilateral tubal occlusion.
      v) Vasectomized partner (provided that the partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of surgical success).
   b) Male subjects with a female partner of childbearing potential must agree to use condoms for the entire Treatment Period AND for 90 days following the final dose of investigational medicinal product (IMP). Female partners are encouraged to use contraception as outlined in Inclusion 7a) from the Screening Visit until the end of the trial. Hormonal contraception that contains estrogen including ethinylestradiol is acceptable for the female partner.

8) Subjects who are not fertile or not sexually active, as defined below, do not require contraception.
   a) Subjects 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 subject.
   b) Male subjects who are surgically sterile (e.g. vasectomized with medical assessment of surgical success).
   c) Female subjects who are surgically sterile (e.g. status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months.
9) Subjects must be able to swallow trial tablets whole.
10) Subjects assessed by the Investigator must be able to appropriately receive and store IMP, and be able to read, understand, and complete the eDiary.
11) Investigator believes that the subject is willing and able to adhere to all protocol requirements.
12) Subject provides signed informed consent and is willing and capable of complying with trial requirements and procedures.

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 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) after the Screening Visit or within 7 days prior to randomization.
5) Use of narrow therapeutic index drugs metabolized by CYP3A4 or CYP2C9 or transported by OAT1, OCT2, and OATP1B1 starting at screening, as determined by the Investigator.
6) Use of strong CYP3A4 inhibitors and inducers during participation in the trial, starting at the Screening Visit.

   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.
7) Inadequate organ function including but not limited to:

a) Alanine aminotransferase (ALT) > 2x 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
f) eGFR <60 mL/min

8) Any clinically significant comorbidity or systemic dysfunction that, in the opinion of the Investigator, would jeopardize the safety of the subject by participating in the trial.
9) History of substance abuse or dependence that would interfere with the completion of the trial, as determined by the Investigator.
10) Known hypersensitivity to KVD824 or placebo or to any of the excipients.
11) Any prior use of any gene therapy treatment for HAE.
12) Participation in any interventional investigational clinical trial, 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 subject.

10. INVESTIGATIONAL MEDICINAL PRODUCT

For clinical trial use, KVD824 has been formulated as 300 mg modified-release tablets.

The active ingredient in the tablets is KVD824. It is present as the hydrochloride salt. All doses refer to freebase equivalent.

Further information about KVD824 300 mg modified-release tablets and matching placebo can be found in the IB.

10.1 Investigational Medicinal Product Administration

Subjects will be randomized in 1:1:1:1 fashion to receive one of the following treatments to be taken twice daily:

- 300 mg (1 x 300 mg tablet) KVD824 (total daily dose [TDD] of 600 mg)
- 600 mg (2 x 300 mg tablets) KVD824 (TDD of 1,200 mg)
- 900 mg (3 x 300 mg tablets) KVD824 (TDD of 1,800 mg), or
- Matching placebo

The placebo group will receive either 1, 2, or 3 placebo tablets. Randomization will be stratified by the number of Investigator-confirmed HAE attacks during the Run-in Period (i.e. ≤3 attacks/4 weeks or >3 attacks/4 weeks).

During the Randomization Visit, arrangements will be made to dispense to the subject blinded IMP for 12 weeks of IMP administration. The IMP will be shipped directly to the subject via a courier service or will be dispensed at the study clinic as required by local regulations or per the site's local practice, as described in the Pharmacy Manual.

Subjects will be instructed to take their first dose with their next morning meal after receipt of the IMP. Subjects will be instructed to take IMP twice daily, approximately 12 hours apart with their morning and evening meals.

No IMP dose modifications are allowed in this trial.

10.2 Packaging and Labeling

The investigational products (i.e. KVD824 or placebo) will be packaged and labeled according to current International Conference on Harmonisation (ICH) Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and national legal requirements. The IMP will be packaged in appropriately labeled High Density Polyethylene (HDPE) containers.

Subjects will be provided with instructions concerning the storage of the IMP at home.

10.3 Storage and Drug Accountability

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

IMP will only be dispensed to the identified subjects 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 unused IMP at Week 2, Week 6, and Week 12/Early Termination (ET) visits.

IMP that has been dispensed to a subject and returned unused must not be re-dispensed for a different subject. 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 or sent for destruction.

10.4 Trial Medication Compliance

Subjects will be provided with instructions on IMP administration and the relevant documentation thereof. In addition, subjects will bring their unused IMP to every in-clinic trial visit. Drug accountability will be reviewed at in-clinic or home health visit (via review of unused IMP), and re-training will occur, if necessary. If in-clinic visits cannot occur the accountability will occur during the home health visit. If a home health visit occurs for Week 12/ET, arrangements will be made to return any unused IMP.

11. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

11.1 Subject Numbers Identification

Each subject will receive a unique subject identification number.

11.2 Randomization Scheme

Subjects will complete a Randomization Visit during which they will be randomized on a 1:1:1:1 basis to receive 300, 600, or 900 mg KVD824 or matching placebo. It will be ensured that a balanced number of subjects assigned placebo receive either 1, 2, or 3 tablets.

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

11.3 Blinding

Subjects, Investigators, and site personnel will not be blinded to the number of tablets a subject is assigned (1, 2, or 3 tablets) but will be blinded to the treatment administered until the trial is complete and the database is locked. A double-dummy design could not be incorporated, as stability with mixed blister packaging was not available for this proof-of-concept trial and using multiple bottles for each dose to allow a double-dummy design would add significant risk of increasing the potential for dosing errors. The potential for dosing errors is more significant than potential bias introduced by the knowledge of the dose level (i.e. number of tablets). Lastly, other trials in HAE have utilized a trial design with the dose level unblinded and the treatment (i.e. active vs. placebo) blinded.

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 subject'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 Medical Monitor prior to breaking the blind.

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

The Investigator will be able to unblind a subject at any time by logging into the Rave Randomization and Trial Supply Management (RTSM) system, selecting the correct subject number, and selecting the unblind option. Following the unblinding of the IMP for a subject, the Investigator should inform the Sponsor and Medical Monitor. In addition to this, the date, time, and reason for unblinding must be recorded in the Rave RTSM system.

If an Investigator, site personnel performing assessments, or subject, 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 subject to the analysis sets has been completed.

12. PERMITTED THERAPIES AND PROHIBITED THERAPIES

12.1 Permitted Therapies

Treatment of HAE attacks during the trial, including the Run-in Period, are to be managed per the Investigator's conventional care of their subjects, including use of on-demand therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an on-demand therapy but not as a long or short-term prophylaxis. Administration of the investigational product and trial procedures will continue without alteration to the protocol-specified schedule even if the subject requires an on-demand treatment for an HAE attack during the trial.

12.2 Prohibited Therapies

Subjects must cease any current medications being taken for HAE prophylaxis throughout the trial. Medications and therapies that preclude a subject from enrolling in the trial are listed in Section 9.2.

The following therapy is NOT permitted throughout the trial (i.e. from Screening Visit until after the final trial visit [Week 12/ET Visit]):

- Long or short-term prophylaxis for HAE including:
  - C1-INH for prophylaxis (e.g. Haegarda, Cinryze, Berinert, Ruconest)
  - Lanadelumab
  - Attenuated androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone)
    - In addition, the subject's last dose of attenuated androgens must be at least 28 days prior to first dose of IMP.
  - Anti-fibrinolytics (e.g. tranexamic acid)
  - Berotralstat
  - 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
- Strong CYP3A4 inhibitors and inducers (see Section 9.2 for list of medications)
- Narrow therapeutic index drugs metabolized by CYP3A4 or CYP2C9 or transported by OAT1, OCT2, and OATP1B1, as determined by the Investigator, are also prohibited throughout the trial.

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. SUBJECT DISCONTINUATION

Subjects 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 subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

The subject 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 subject compliance to trial visits/procedures, lost to follow-up).

The Investigator will discontinue a subject from the trial for the reasons listed below if the event is determined to be related to IMP; clinically significant laboratory findings must be confirmed:

- ALT or AST > 3 times ULN and with either direct bilirubin > 2 times ULN or INR increased from baseline and is > 1.5 times ULN, or
- Any SAE or a clinically significant Grade 4 adverse event (note: a clinically significant Grade 4 laboratory abnormality is considered a Grade 4 adverse event).

If a subject is discontinued from the trial, every attempt will be made to complete and document the ET visit as soon as possible. If the subject is discontinued from the trial after receiving IMP, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the Investigator to complete other trial assessments. Subjects 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 subject 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 subjects will not be replaced; subject/randomization numbers will not be reused.
If a subject does not complete a scheduled visit, every effort should be made to contact the subject to reschedule the visit. All efforts should be documented in the subject's medical source record. A subject will be considered lost to follow-up if subject cannot be reached after 4 weeks from the scheduled visit.

14. TRIAL STOPPING CRITERIA

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the trial continues, the trial may be terminated after appropriate consultation between the relevant parties.

The trial will be terminated if the following occur and are determined to be related to IMP by the treating Investigator:

- Death in any subject.
- The occurrence in any subject of a life-threatening SAE not related to HAE.
- Liver-related AE that meets Hy's Law in more than 1 subject (FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009; Zimmerman, 1968):
    1. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3× the upper limit of normal (ULN)
    2. Total bilirubin (TBL) elevation of >2× ULN
    3. Absence of initial findings of cholestasis (i.e., absence of elevation of alkaline phosphatase [ALP] to >2× ULN)
    4. No other reason can be found to explain the combination of increased ALT and TBL, such as viral hepatitis A through E; other preexisting or acute liver disease; or another drug capable of causing the observed injury.
- Similar Grade 3 or higher AE, excluding liver-related AE, in more than 1 subject (note: clinically significant Grade 3 laboratory abnormalities are considered Grade 3 AEs, clinically significant laboratory findings must be confirmed).

15. ASSESSMENTS

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

15.1 Subject 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; therapies and supplements taken within the past 4 weeks; and participation in interventional clinical studies in the past 4 weeks.

15.2 Efficacy Assessments

15.2.1 Investigator-Confirmed HAE Attack

When an attack of HAE occurs, the subject will provide a description of the HAE attack in the Subject eDiary. Should a subject become incapacitated during an attack and unable to record details, this information can be recorded once the incapacitation has resolved. This description will include:

- Start and stop date/time of each attack
- Location(s) of each attack
- Symptom(s) including prodromal
- Impact on activity
- Use of conventional treatment of each attack
- Subject assessment of attack severity

As soon as possible following the completion of each attack and within no more than 5 working days, contact will be made between the site staff and the subject to confirm, clarify, and correct any recorded eDiary data. Site staff who collect the HAE attack information from the subject must be designated and qualified to perform this task. Additionally, the designated site staff will ask questions about each attack to assist the Investigator (or qualified designee) with their confirmation of each attack. The investigator (or qualified designee) will rate the severity of each attack according to the following scale:

- Mild
- Moderate
- Severe

The Investigator (or qualified designee) will assess whether the reported attack was caused by HAE. To be classified as an Investigator-confirmed HAE attack, the event must have symptoms or signs consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region.
- Abdominal angioedema: abdominal pain with or without abdominal distention, nausea, vomiting, or diarrhea.

- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx.

Despite the presence of these symptoms, the Investigator may clinically determine that the event did not represent an HAE attack if there are features that strongly refute such a diagnosis. For example, the reported event is accompanied by symptoms that are not consistent with an HAE attack (e.g. urticaria), the reported event persists well beyond the typical time course of an HAE attack, or there is a likely alternate etiology for the event (e.g. the subject's abdominal symptoms are attributable to a viral gastroenteritis).

The collection, reporting, and assessment of attacks in this trial will be done in accordance with KalVista's HAE Attack Document (K-HAD). Site personnel will be trained on the K-HAD prior to screening subjects at their site.

15.2.2 Angioedema Control Test (AECT)

The AECT is a validated, self-administered, retrospective 4-item patient-reported outcome measure for patients with recurrent angioedema used to quantify disease control and to aid treatment decisions (Weller et al. 2020). The questionnaire addresses the frequency of angioedema, angioedema-related quality-of-life (QoL) impairment, unpredictability of angioedema attacks, and angioedema control by the current treatment approach. Each of the 4 AECT items is scored from 0 to 4 points with higher scores indicating a higher level of angioedema control. The AECT score is calculated by summing up all 4 item scores, with a minimum and maximum possible score of 0 and 16 points. AECT will be collected per the Schedule of Events (Table 1).

1. In the last 4 weeks, how often have you had angioedema?
2. In the last 4 weeks, how much as your quality of life been affected by angioedema?
3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?
4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?

15.2.3 Angioedema Quality of Life Questionnaire (AE-QoL)

The AE-QoL is a symptom-specific health-related QoL instrument for patients with recurrent angioedema. It consists of 17 items that can be grouped together to a total score or to 4 different domain scores ("Functioning," "Fatigue/Mood," "Fears/Shame," and "Food") that collectively evaluate the extent of angioedema-dependent QoL impairment during the previous 4 weeks. Each AE-QoL question has 5 answer options (scored 1-5), with lower and higher scores indicting less and more adverse impact, respectively. The total score is calculated, which is then transformed into a linear scale that ranges from 0 to 100, with a score of 100 indicating the worst possible impairment. A minimal clinically important difference of 6 points has been described (Weller et al. 2012, Weller et al. 2016). AE-QoL will be collected per the Schedule of Events (Table 1).

15.2.4 Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a psychometrically sound and valid measure of the major dimensions of patients' satisfaction with medication (Atkinson et al. 2004). The questionnaire comprises 14 questions that are scaled on a 7-point bipolar scale ranging from "Extremely Satisfied" to "Extremely Dissatisfied." TSQM will be collected per the Schedule of Events (Table 1).

- How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

- How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
- How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
- As a result of taking this medication, do you currently experience any side effects at all?
- How bothersome are the side effects of the medication you take to treat your condition?
- To what extent do the side effects interfere with your physical health and ability to function (i.e. strength, energy levels, etc.)?
- To what extent do the side effects interfere with your mental function (i.e. ability to think clearly, stay awake, etc.)?
- To what degree have medication side effects affected your overall satisfaction with the medication?
- How easy or difficult is it to use the medication in its current form?
- How easy or difficult is it to plan when you will use the medication each time?
- How convenient or inconvenient is it to take the medication as instructed?
- Overall, how confident are you that taking this medication is a good thing for you?
- How certain are you that the good things about your medication outweigh the bad things?
- Taking all things into account, how satisfied or dissatisfied are you with this medication?

15.3 Safety Assessments

15.3.1 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.

15.3.2 Vital Signs

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

15.3.3 12-Lead Electrocardiogram (ECG)

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

15.3.4 Clinical Safety Laboratory Assessments

Blood samples (approximately 60 mL) will be taken using standard venipuncture techniques. The central laboratory will provide a Laboratory Manual with detailed procedures. Safety labs will be collected per the Schedule of Events (Table 3).

Table 3: 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 eGFR Urea, Blood Nitrogen 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 subjects of childbearing potential. HCG Qualitative		

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HbA1c=glycosylated hemoglobin; GGT=gamma glutamyl transferase; eGFR=estimated glomerular filtration rate HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; 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 subject eligibility prior to randomizing the subject. 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. Clinically significant laboratory abnormalities, as determined by the treating Investigator, will be recorded as adverse events after the start of KVD824 dosing.

16. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

16.1 Adverse Events

Any untoward medical occurrence in a subject or clinical investigation subject 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.

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 subject upon questioning.

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

16.2 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 subject or might require intervention to prevent one of the other).

16.3 Time Period and Frequency for Collection

The period of observation for AEs extends from the time of the subject's first dose of IMP until the Week 12/ET Visit. The period of observation for SAEs extends from the time of signing the informed consent until the Week 12/ET Visit. Ongoing AEs/SAEs at the Week 12/ET Visit will be followed up until the event has resolved or is considered chronic or stable or the event has been clearly shown to be unrelated to the IMP. Any relevant diseases occurring between the Screening Visit and the first dose of IMP are to be captured as medical history unless it is determined to be an SAE.

16.4 Method of Detection

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

16.5 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 subject. 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)

16.6 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.

16.7 Reporting

16.7.1 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.

16.7.2 Reporting Serious Adverse Events

All SAEs, regardless of relationship to the IMP, must be immediately reported within 24 hours of awareness by any site staff. If it is not possible to complete all sections of the SAE form within 24 hours of becoming aware of the SAE, transmission of the form must not be delayed, and the outstanding information should be sent on a follow-up SAE form. All information relevant to the SAE must be recorded.

The Investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the SAE form. All subjects experiencing a SAE must be followed up and the outcome reported.

SAE forms are to be submitted to kalvista.safety@arriello.com or sent by fax to +1 888 215 1304 (North America) or +420 296 181 216 (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 subject; 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.

16.7.3 Reporting Suspected Unexpected Serious Adverse Reactions

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

- Serious: as defined in Section 16.2 of this protocol.
- Unexpected: AE is not consistent with the Reference Safety Information (found in the Investigator's Brochure).
- Suspected: relationship to IMP is suspected to be related as defined in Section 16.6 of this protocol.

All SUSARs should be reported to the relevant Regulatory Authority, EC/IRB, and investigators as per the regulatory requirement and timelines.

16.8 Pregnancy

Preliminary dose range finding embryofetal development toxicity studies indicate that KVD824 was generally well tolerated (noting that excessive body weight loss is evident at high dose levels).

A female subject who becomes pregnant while participating in the trial must notify the Investigator immediately. The subject 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 subject 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 kalvista.safety@arriello.com. 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 subject was discontinued from the trial or if the trial has finished.

If a female partner of a male trial subject 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 subjects who become pregnant during the trial.

16.9 Treatment of Overdose

No specific antidote to KVD824 is known and treatment of overdose should be supportive.

17. TRIAL PROCEDURES

KOMPLETE will be conducted on an outpatient basis and will comprise in-clinic visits. If in-clinic visits cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the subject from attending the in-clinic visits), 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 subject 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.

If a home health visit cannot be conducted (e.g. due to country restrictions or quarantine), then a televisit should be performed followed by a visit to occur as soon as is reasonably possible. The televisit could entail the use of an interactive audio and video telecommunications system that permits real-time communication between the site and subject at home, or it could entail a telephone call.

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

Informed consent must be obtained for all subjects 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).

17.1 Screening Period

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

The Screening Period includes an outpatient Screening Visit followed by a Run-in Period. Procedures for the Screening Visit may take place on different days; however, all procedures should be completed within 4 weeks of starting the visit. All subjects will sign an Informed Consent Form (ICF) prior to any trial-related procedures being performed. Consent may be collected through a remote e-consenting solution if allowed through country and site regulations. Following full discussion of the trial and the signing of the ICF, a subject 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 subjects without genetic confirmation of HAE Type I or II.
- Full medical history (Section 15.1), including any relevant previous and concurrent diseases, HAE disease history; therapies and supplements taken within the past 4 weeks; and previous participation in interventional clinical studies in the past 4 weeks.
- Demographic information including year of birth; race and ethnicity (if allowed); and sex (Section 15.1).
- Height (m; without shoes) and weight (kg) (Section 15.1). Body mass index will be calculated.
- Complete physical examination (Section 15.3.1).

- Vital signs (SBP and DBP, PR, and RR). BP and PR recorded after subject has been resting for at least 5 minutes (Section 15.3.2).
- 12-lead ECG after subject has been supine for at least 5 minutes (Section 15.3.3).
- AE-QOL Questionnaire (Section 15.2.3).
- AECT Questionnaire (Section 15.2.2).
- Serum pregnancy test (female subjects of childbearing potential).
- Blood and urine samples for clinical laboratory tests (Section 15.3.4).
- Subject eDiary training on the requirements for reporting attacks, and information subjects will be expected to provide in the eDiary. The subject will confirm understanding of what is required for reporting attacks.

17.1.2 Run-In Period

Screened subjects will enter a Run-in Period of up to 8 weeks in duration. The start of the Run-in Period is determined by the type of HAE therapy being used by the subject at the time of Screening, as follows:

- **Use of On-demand Therapy Only for Treatment of HAE Attacks:** Subjects using only on-demand therapy will enter the Run-in Period upon completion of Screening Visit eDiary assessments.
- **Use of Prophylaxis Therapy for Treatment of HAE Attacks:** Subjects using any prophylaxis therapy will enter the Run-in Period following the first Investigator-confirmed HAE attack after discontinuation of all prophylactic therapy. This attack does not count towards the total attacks required to meet the run-in eligibility criteria. Subjects must enter the Run-in Period within 8 weeks of completion of Screening Visit the eDiary assessments.

Treatment of HAE attacks during the trial, including the Run-in Period, are to be managed per the Investigator's conventional care of their subjects, including use of on-demand therapies that the Investigator deems as medically appropriate.

As soon as possible following the completion of each attack and within no more than 5 working days, contact will be made between the site staff and the subject to confirm, clarify, and correct any recorded eDiary data. Site staff who collect the HAE attack information from the subject must be designated and qualified to perform this task. Additionally, the designated site staff will ask questions about each attack to assist the Investigator (or qualified designee) with their confirmation of each attack. The investigator (or qualified designee) will rate the severity of each attack.

During the Run-in Period all subjects must meet one of the following eligibility criteria:

- Two Investigator-confirmed attacks in the first 4-week period.
- Three Investigator-confirmed attacks in ≤8 weeks.

Once the above Run-in Period criterion is met subjects may proceed to the Randomization Visit.

Subjects who do not meet the Run-in Period criterion will be ineligible to randomize and will not be allowed to re-screen.

17.2 Randomization Visit (In-Clinic or Home Health Visit)

The Randomization Visit will be an in-person, outpatient visit, and will occur within approximately 10 days of completing the Run-in Period.

Subjects will be randomized in 1:1:1:1 fashion to receive one of the following treatments:

- 300 mg (1 x 300 mg tablet) KVD824
- 600 mg (2 x 300 mg tablets) KVD824
- 900 mg (3 x 300 mg tablets) KVD824
- Matching placebo

It will be ensured that a balanced number of subjects assigned placebo receive either 1, 2, or 3 tablets.

Arrangements will be made to dispense to the subject blinded IMP for twice daily oral self-administration for 12 weeks. The IMP will be shipped directly to the subject via a courier service or will be dispensed at the study clinic as required by local regulations or per the site's local practice, as described in the Pharmacy Manual.

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).
- Symptom-directed physical examination (Section 15.3.1).
- Vital signs (SBP and DBP, PR, and RR). BP and PR recorded after subject has been resting for at least 5 minutes (Section 15.3.2).
- 12-lead ECG after subject has been supine for at least 5 minutes (Section 15.3.3).
- Blood and urine samples for clinical laboratory tests (Section 15.3.4).
- Serum pregnancy test (female subjects of childbearing potential).
- Subject eDiary re-training, if necessary.
- Concomitant medication review.
- Randomize subject 1:1:1:1 to receive 300, 600, or 900 mg KVD824 or matching placebo.
    - Randomization may occur prior to the Randomization Visit if the site will be dispensing IMP during the in-clinic Randomization Visit; however, Run-in eligibility must be confirmed prior to randomizing the subject.
- Make arrangements to dispense the assigned IMP to subjects.

17.3 Treatment Period

The Treatment Period is 12 weeks in duration and starts with the first dose of IMP. Subjects will be instructed to take their first dose with their next morning meal after receipt of the IMP. During the Treatment Period, subjects will self-administer IMP twice daily approximately 12 hours apart with their morning and evening meals in accordance with their randomized assignment. Both the Investigator and subject will be blinded to the assigned treatment, but not to the number of tablets assigned (1, 2, or 3 tablets).

Treatment of HAE attacks is to be managed per the Investigator's conventional care of their subjects, including use of on-demand therapies that the Investigator deems as medically appropriate. Use of C1-INH will be permitted as an on-demand therapy but not as a long or short-term prophylaxis. Administration of the investigational product and trial procedures will continue without alteration to the protocol-specified schedule even if the subject requires an on-demand treatment for an HAE attack during the trial.

When an attack of HAE occurs, the subject will provide a description of the HAE attack in the Subject eDiary and will be assessed by trial staff as outlined in Section 15.2.1.

Visits should occur within 3 days of Week 2, 4, and 6. The Week 12/ET Visit should occur within 7 days after the final dose of IMP.

Subjects will complete the AE-QOL Questionnaire (Section 15.2.3) and the AECT Questionnaire (Section 15.2.2) at Screening Visit, 4 and 8 weeks after the start of dosing, and the final dose. TSQM will be completed after the final dose (Section 15.2.4).

17.4 Week 2 and 6 (In-clinic or Home Health Visit)

During the Week 2 and Week 6 visit, the following activities will be performed:

- Vital signs (SBP and DBP, PR, and RR). BP and PR recorded after subject has been resting for at least 5 minutes (Section 15.3.2).
- 12-lead ECG after subject has been supine for at least 5 minutes (Section 15.3.3).
- Blood and urine samples for clinical laboratory tests (Section 15.3.4).
- Serum pregnancy test (female subjects of childbearing potential).
- Subject eDiary reviewed with re-training, if necessary.
- IMP accountability.
- Concomitant medication review.
- AEs recorded (Section 16).

17.5 Week 4 (Brief In-clinic/Site lab Visit or Home Health Visit)

During the Week 4 visit, a single safety lab sample will be drawn to assess liver enzymes and clinical chemistry (Section 15.3.4). This sample can be obtained at a brief in-clinic or site lab visit or can be obtained by a Home Health service provider.

17.6 Week 12/Early Termination (In-Clinic or Home Health Visits)

At the Week 12/ET Visit the subject will return to the clinic for the final visit at which the following procedures will be conducted:

- Symptom-directed physical examination (Section 15.3.1).
- Vital signs (SBP and DBP, PR, and RR). BP and PR recorded after subject has been resting for at least 5 minutes (Section 15.3.2).
- 12-lead ECG after subject has been supine for at least 5 minutes (Section 15.3.3).
- Blood and urine samples for clinical laboratory tests (Section 15.3.4).

- Serum pregnancy test (female subjects of childbearing potential).
- Return IMP (or arrange for return if in-clinic visit is not possible).
- AE-QOL Questionnaire collected with the last dose of IMP (Section 15.2.3).
- AECT Questionnaire collected with the last dose of IMP (Section 15.2.1).
- TSQM Questionnaire collected with the last dose of IMP (Section 15.2.4).
- Concomitant medication review.
- AEs recorded (Section 16).

18. STATISTICAL CONSIDERATIONS

18.1 Sample Size Determination

A total sample size of approximately 48 subjects (~12 randomized per dose-level) will provide at least 90% power to detect a 70% reduction in the monthly rate of attacks, between each active dose and placebo, using a two-sided 5% test, adjusted with Bonferroni correction. This assumes an average of at least 2 attacks/4 weeks on placebo and a Poisson distribution with approximately 90% subjects completing the 12 weeks. This sample size will also provide more than 80% power to detect a smaller effect of 50% reduction in attack rate. In addition, this sample size also ensures nearly 90% power to detect a 70% reduction should the attack rate in the placebo group be lower than expected at 1 attack/4 weeks. It is assumed that the rate of HAE attacks follows a Poisson distribution, therefore, the test for the ratio of two Poisson rates was used for the sample size calculation, however, negative binomial regression is used as a primary analysis to correct for potential overdispersion in the model. Sample size calculations were performed using PASS v20.0.3.

18.2 Estimands and Intercurrent Events

Intercurrent event types (IcEVs) are displayed in Table 4 and estimand(s) with rationale for strategies to address IcEVs are summarized in Table 5.

Table 4: Intercurrent Event Types

Label	Intercurrent Event Type
IcEV1 (Death)	Death from any cause.
IcEV2 (Discontinue TEAE)	Discontinuation of IMP due to TEAE or tolerability issue.
IcEV3 (Discontinue LOE)	Discontinuation of IMP due to LOE where HAE symptoms are at an unacceptable level.
IcEV4 (Prohibited medications)	Use of prohibited medications that may interfere with outcome (Section 12.2).
IcEV5 (Treatment change)	Switch of treatments, or sustained use of other prophylactic medications either instead or as additional treatment (i.e. taken for the purpose of prophylaxis rather than treating HAE attacks).
IcEV6 (Discontinue logistical)	Discontinuation of IMP due to reasons unrelated to treatment such as logistical issues (e.g. during pandemic, personal reasons such as moving area or burden of clinic visits).

Abbreviations: HAE=hereditary angioedema; IcEV=Intercurrent event types; IMP=investigational medicinal product; LOE=lack of efficacy; TEAE=treatment emergent adverse event.

Table 5: Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Estimand Label	**Primary Estimand**
Estimand Description	Rate ratio of Investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo)) in subjects with a confirmed diagnosis of HAE Type I or II who have at least 1.5 attacks per 4 weeks while off prophylactic treatment. Number of attacks will be measured 'while on treatment' over up to 12 weeks or until their treatment stops or changes (expressed as number of attacks on treatment). Subjects receive on-demand conventional care for HAE attacks but receipt of additional treatments as a prophylactic would constitute a change and the end of the period considered 'while on treatment.'
Target Population	Subjects with a confirmed diagnosis of HAE Type I or II who have at least 1.5 attacks per 4 weeks while off prophylactic treatment and would meet other trial inclusion criteria.
Endpoint	Rate of Investigator-confirmed HAE attacks during the Treatment Period.
Treatment Condition(s)	Twice daily oral self-administration: prophylactic KVD824 doses versus Reference: placebo, on top of conventional care including on-demand treatment for an HAE attack.
Population-Level Summary	Rate ratio of HAE attacks while on treatment (each of the KVD824 dose groups versus placebo).
Intercurrent Event Strategy	
IcV1 (Death)	While on treatment.
IcEV2 (Discontinue TEAE)	While on treatment.
IcEV3 (Discontinue LOE)	While on treatment.
IcEV4 (Prohibited medications)	While on treatment.
IcEV5 (Treatment change)	While on treatment.
IcEV6 (Discontinue logistical)	While on treatment.
Rationale for Strategies	The primary focus of this phase 2 trial is to evaluate the attack rate over a period while on assigned treatment prior to the occurrence of intercurrent events without use of prohibited medications or additional prophylactic treatments. In the case of an unacceptable level of attacks or tolerability issues resulting in changes to treatment, the measurement period ends.

Abbreviations: HAE= hereditary angioedema; IcEV=Intercurrent event types; IMP=investigational medicinal product; LOE=lack of efficacy; TEAE=treatment emergent adverse event.

18.3 Populations for Analyses

- Screened Set includes all subjects who have signed informed consent.
- Enrolled Set includes all subjects who have signed informed consent and begun the Run-In Period.
- Randomized Set includes all subjects who are randomized.
- Safety Set (SAF) will include all subjects who are randomized and receive at least one dose of IMP.

- Full Analysis Set (FAS) will include all subjects who are randomized, receive at least 1 dose of IMP, and have post baseline HAE diary data recorded. Subjects will be analyzed according to randomized treatment. The FAS population will be the population for efficacy analyses.
- Per-protocol Set (PPS) includes all subjects from FAS who complete 12 weeks and who do not have pre-defined major protocol deviations that may affect primary efficacy endpoint.

18.4 General Considerations

The statistical analysis plan (SAP) and associated templates for tables, listing and figures will be developed in a separate document that will provide a technical and detailed elaboration of the principal features stated in the protocol and will be developed and finalized prior to trial unblinding. Any deviations from the planned analyses will be described and justified in the final Clinical Study Report (CSR).

Summary tables, figure and listings will be created using Version 9.4 (or later) of the SAS® software for Microsoft Windows (SAS Institute, Inc., Cary, North Carolina).

The following descriptive statistics will be provided depending on the nature of considered data:

- **Qualitative data**: number of observed values, number and percentage of subjects per category.
- **Quantitative data**: number of observed values, mean and standard deviation (SD), median, first and third quartiles, minimum, and maximum.

All statistical tests will be 2-sided with an alpha of 0.05. The primary efficacy endpoint analysis will have Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests will be 2-sided with an alpha of 0.0167. The analysis of the secondary or exploratory endpoints will not have multiplicity adjustments.

There are 4 treatment groups in the trial:

1. subjects received 300 mg (1 x 300 mg tablet) KVD824
2. subjects received 600 mg (2 x 300 mg tablet) KVD824
3. subjects received 900 mg (3 x 300 mg tablet) KVD824
4. subjects received placebo (all subjects who received matching placebo of 1, 2 or 3 tablets)

18.4.1 Bonferroni Multiplicity Adjustment

Bonferroni adjusted significance level is obtained by dividing the original significance level 0.05 by the number of comparisons on the attack rate between each KVD824 dose level and placebo (i.e. the adjusted significance level is 0.0167 [0.05 divided by 3]).

18.5 Analysis of Disposition

Subject disposition will be presented for all subjects. The number and percentage of subjects who have been randomized and included in SAF, FAS, and PPS will be presented by treatment group and overall.

The number and percentage of subjects who prematurely discontinued during the trial will be presented for each treatment group and overall, for SAF and FAS. Primary reasons for premature discontinuation from the trial will be summarized by treatment group and overall, for SAF and FAS. Subject disposition,

subjects completing and terminating the trial, and trial analysis sets will be listed by subject for all subjects in the Enrolled Set.

18.6 Demographics and Baseline Characteristics

Demographic data and baseline characteristics including age, sex, race, ethnicity, height at screening, weight at screening, and body mass index (BMI) at screening will be summarized by treatment group using descriptive statistics for the SAF and FAS. Baseline attack rates (calculated as the number of attacks occurred during the Run-in Period adjusted by time), medical history, HAE history, prior and concomitant medication will be summarized by treatment group for the SAF and FAS.

18.7 Statistical Analysis of Efficacy Endpoints

18.7.1 Primary Endpoint(s)

Primary analysis hypothesis: The null hypothesis is that the rate ratio of investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo) is 1 (no difference between active dose and placebo treatment groups) versus the alternative hypothesis that the rate ratio of investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo) is not 1.

Table 6 gives a summary of analysis methods, strategy for handling missing data, and sensitivity analysis for the primary endpoint.

Table 6: 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	Rate ratio of investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo) in subjects with a confirmed diagnosis of HAE Type I or II who have at least 1.5 attacks per 4 weeks while off prophylactic treatment. Number of attacks will be measured 'while on treatment' over up to 12 weeks or until their treatment stops or changes. Subjects may receive on-demand conventional care for HAE attacks but receipt of additional treatments as a prophylactic would constitute a change and the end of the period considered 'while on treatment.'	FAS	Data after occurrence of intercurrent events will not be utilized.	Negative binomial regression with randomization stratification factor of baseline attack rate per 4 weeks during run-in period as a fixed covariate and treatment as a fixed factor and the logarithm of time each subject was observed 'while on treatment' will be used as an offset variable in the model. This model will be used to estimate rate of HAE attacks while on treatment and rate ratio of HAE attacks (each of the KVD824 dose groups versus placebo) with 95% confidence interval and 2-sided p-value.	Sensitivity: For subjects who discontinue prematurely from Treatment Period or with the data censored after an intercurrent event, the remaining part of the Treatment Period will be imputed 1,000 times using the bootstrap method (Section 18.7.2). The same analysis method, negative binomial regression model will be performed on 1,000 imputed bootstrap samples. The results from the individual models will be combined using Rubin's formulae from PROC MIANALYZE. Supplementary: repeat primary analysis on PPS.

Abbreviations: FAS=Full Analysis Set; HAE=hereditary angioedema; PPS=Per Protocol Set.

18.7.2 Multiple Imputation Analysis

Analysis based on imputing missing values by drop out reason is the sensitivity analysis to the primary efficacy analysis. The primary imputation method within this sensitivity analysis is described below.

A subject is considered to have missing values in case he/she discontinues treatment prematurely and does not finish the Treatment Period or has an IcEV making the data collected after the IcEV considered irrelevant.

Fraction of non-missing data (F) during the Treatment Period is defined as the number of participation days divided by 84 (12 x 7 – scheduled length of the 12 weeks Treatment Period).

The **observed number of HAE attacks** ($NA_{observed}$) is the number of HAE attacks recorded in the eDiary and observed during the Treatment Period when the subject was on treatment and prior to an intercurrent event.

The **missing number of HAE attacks** ($NA_{imputed}$) which will be imputed as the number of HAE attacks over 12 weeks then adjusted (1 – F) to take into account the fraction of time observed, i.e. to derive the number of HAE attacks which would have occurred between drop out and Week 12.

The **complete number of HAE attacks** ($NA_{complete}$) which will be used for the sensitivity analysis will be calculated as

$$NA_{complete} = (1 - F) \times NA_{imputed} + NA_{observed}. \text{ (Equation 1)}$$

and rounded up to the nearest integer.

If a subject discontinues prematurely from the Treatment Period, the remaining part of this period will be imputed using the bootstrap method:

1) Draw a bootstrap sample with replacement from all FAS subjects of the same treatment group with no missing values (the subjects completed 12 weeks Treatment Period) using PROC SURVEYSELECT.
2) Use the following rules to calculate the number of **missing HAE attacks** ($NA_{imputed}$) for the missing data for each bootstrap sample:
    a) Missing data are considered as missing at random (MAR) if the dropout reasons / intercurrent events are not related to the IMP (e.g. site closure, personal reasons). For subjects with MAR data, the value of missing number of HAE attacks ($NA_{imputed}$) will be the median of $NA_{observed}$ of all subjects who have complete data within the same treatment group.
    b) Data which are missing due to dropout/intercurrent event for the following reasons are considered missing not at random (MNAR): discontinued due to IMP-related AEs, death, or lack of efficacy. For subjects with MNAR data, the median ($\tilde{x}$) of the worst 25% observed data of the bootstrap sample from subjects who have complete data within the same treatment group will be determined. The value of the $NA_{imputed}$ equals the maximum $NA_{observed}$ among all these subjects if $NA_{observed} > \tilde{x}$, and $\tilde{x}$ otherwise.
    c) Data which are missing because of protocol violations, other, withdrawal by subjects or physician decision will be reviewed, and a decision of classifying them into the categories as described in a) or b) will be made and documented prior to unblinding.

3) After $NA_{imputed}$ is calculated, the complete number of HAE attacks will be calculated using Equation 1 as $NA_{complete} = NA_{imputed} + NA_{observed}$. The complete bootstrap sample with imputed values ($NA_{complete}$) will be analyzed by fitting the primary analysis model.
4) Repeat above 3 steps for 1,000 times.
5) The model summaries will be combined from the 1,000 imputed bootstrap samples using Rubin's rule from PROC MIANALYZE.

18.7.3 Secondary Endpoint(s)

No formal hypotheses will be tested for secondary endpoints. All statistical tests for the secondary efficacy endpoints will be considered of exploratory nature, pairwise comparisons will be performed between each KVD824 dose level and placebo, but no adjustment will be made for multiplicity.

Proportion of subjects without Investigator-confirmed HAE attacks during the Treatment Period will be analyzed using logistic regression with treatment as fixed effect and randomization stratification factor as a fixed covariate in the model. Rate of Investigator-confirmed HAE attacks that require conventional treatment during the Treatment Period will be analyzed using negative binomial regression similar to the primary analysis. AE-QoL total score and domain scores during the Treatment Period and AECT score and domain scores during the Treatment Period will be analyzed using analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Baseline value for the secondary endpoints will be defined as the most recent non-missing measurement collected prior to the first dose of IMP.

Proportion of subjects with an AECT score ≥12 at the end of the Treatment Period will be analyzed using logistic regression with treatment as fixed effect and randomization stratification factor as a fixed covariate in the model.

Additional statistical models may be considered, and details will be provided in the SAP.

18.7.4 Exploratory Endpoint(s)

No formal hypotheses will be tested for exploratory endpoints. All statistical tests for the exploratory efficacy endpoints will be considered of exploratory nature, pairwise comparisons will be performed between each KVD824 dose level and placebo, but no adjustment will be made for multiplicity.

Rate of Investigator-confirmed HAE attacks during the Treatment Period by severity will be analyzed using negative binomial regression similar to the primary analysis including additional fixed covariate for severity. Rate of conventional treatment used during the Treatment Period will be analyzed using negative binomial regression similar to the primary analysis. TSQM total scores at the end of the Treatment Period will be analyzed using ANOVA or ANCOVA. Additional statistical models may be considered, and details will be provided in the SAP.

18.8 Safety Analyses

Safety analyses will be performed by treatment group using the SAF. Safety endpoints include AE, clinical laboratory assessments, vital signs, ECG, and physical examination findings as described in the Sections 15.3 and 16.1.

The AEs and SAEs recorded during the trial will be summarized by system organ class (SOC), preferred term, and treatment group, and will include the total number of events with number and percentage of

subjects with AEs. Adverse events and medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

Summaries of the number and percentage of subjects (and number of events) for AEs, severe AEs, SAEs, AEs with an outcome of death, AEs leading to discontinuation of the trial treatment will be provided.

For physical examination, ECG, and laboratory variables (measured by the central laboratory), the number and percentage of subjects with normal or abnormal results will be presented at each scheduled visits by treatment group. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter by treatment group. Shift tables by treatment group will be provided when appropriate.

18.9 Interim Analyses

Not applicable.

19. TRIAL ADMINISTRATION

19.1 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.

19.2 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.

19.3 Ethics

19.3.1 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.

19.3.2 Informed Consent/Assent

Informed consent/assent will be obtained from the subject 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.

19.3.3 Subject Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be specified on trial documents by their subject ID, not by name. Documents that identify the subject (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 subject authorization or as required by law.

19.4 Data Handling and Record Keeping

19.4.1 Source Documents

All source documents from which eCRF entries are derived should be placed in the subject's trial records. Source documents usually 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 subject confidentiality is maintained.

19.4.2 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 subject. 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.

19.4.3 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.

19.4.4 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.

19.5 Financing and Insurance

19.5.1 Financial Disclosure

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

19.5.2 Trial Insurance

Clinical trial insurance will be maintained per local regulations.

19.6 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.

19.7 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.

19.8 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.

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