

Protocol Number: KVD900-303

Official Title: Open-Label Safety, Pharmacokinetic, and Efficacy Trial of Sebetralstat (KVD900) in Pediatric Patients (Ages 2-11) with Hereditary Angioedema Type I or II

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PROTOCOL TITLE

Open-Label Safety, Pharmacokinetic, and Efficacy Trial of Sebetralstat (KVD900) in Pediatric Patients
(Ages 2-11) with Hereditary Angioedema Type I or II

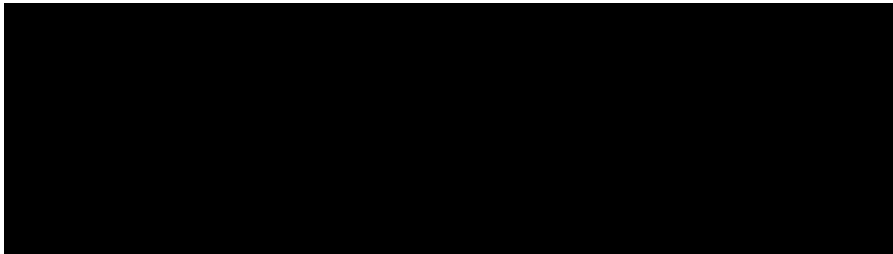
Protocol Number:	KVD900-303
Protocol Name:	KONFIDENT-KID
Compound:	Sebetralstat
Trial Phase:	3
Sponsor:	KalVista Pharmaceuticals Ltd Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom
IND Number:	143807
EUCT Number:	2023-507591-44-00
Date of Protocol:	24 July 2025, Version 3.4 (US Only) 11 February 2025, Version 2.0 4 March 2024, Version 1.0
Compliance:	This trial will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

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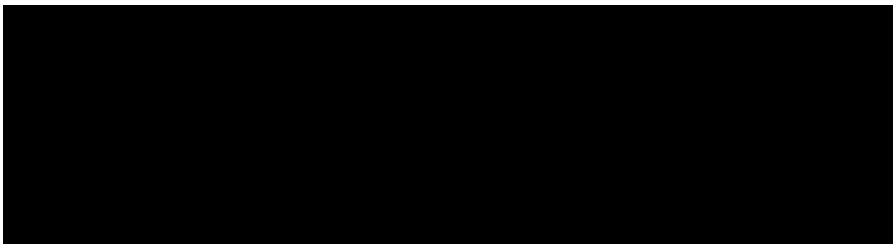
1. SIGNATURE PAGE

Title: Open-Label Safety, Pharmacokinetic, and Efficacy Trial of Sebetralstat (KVD900) in Pediatric Patients (Ages 2-11) with Hereditary Angioedema Type I or II

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



Chief Medical Officer
KalVista Pharmaceuticals Ltd



Vice President, Clinical
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2. DECLARATION OF THE INVESTIGATOR

Title: Open-Label Safety, Pharmacokinetic, and Efficacy Trial of Sebetralstat (KVD900) in Pediatric Patients (Ages 2-11) with Hereditary Angioedema Type I or II

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

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

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

Investigator Signature

Date

Name (block letters)

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

The primary purpose of this amendment is to increase the sebetralstat dose levels to align with the approved US Food and Drug Administration (FDA) labeling for sebetralstat. The changes from Version 2.0 to Version 3.4 of the protocol and the rationale are as follows:

- Increased the dose levels of sebetralstat to be administered in the trial as follows:
 - >45 kg patient weight: 600 mg (2 x 300 mg) orally disintegrating tablet (ODT)
 - 20 to 45 kg patient weight: 300 mg (1 x 300 mg) ODT
 - ≥9.5 to <20 kg patient weight: 150 mg (2 x 75 mg) ODT
- **Rationale:** Dose levels were increased for all weight bands to match a 600 mg equivalent, in alignment with the approved FDA labeling for sebetralstat
- Updated the sebetralstat dosing and administration instructions
 - **Rationale:** Dosing and administration instructions were modified to align with the approved FDA labeling for sebetralstat
- Added a pharmacokinetic (PK) collection visit for patients to obtain PK samples at their new dose level
 - **Rationale:** To obtain PK data for patients at the new dose levels
- Increased enrollment to up to 48 patients enrolled
 - **Rationale:** To allow enrollment of additional pediatric patients to collect PK and attack data at the increased dose level

Other clarifications were added and minor typographical corrections were made that are not described above.

3. SYNOPSIS

Title	Open-Label Safety, Pharmacokinetic, and Efficacy Trial of Sebetralstat (KVD900) in Pediatric Patients (Ages 2-11) with Hereditary Angioedema Type I or II
Trial No	KVD900-303
Protocol Name	KONFIDENT-KID
Phase	3
Trial Centers	Hereditary angioedema (HAE) treatment centers worldwide
Objectives	Primary Objective - To evaluate the safety and tolerability of sebetralstat in pediatric patients with HAE Type I or II. Secondary Objective - To evaluate the pharmacokinetics (PK) of sebetralstat in pediatric patients with HAE Type I or II. - To evaluate the clinical efficacy of sebetralstat for the on-demand treatment of HAE attacks in pediatric patients with HAE Type I or II.
Trial Design & Procedures	KVD900-303 is an open-label, multicenter clinical trial in patients aged 2 to 11 years old with HAE Type I or II. Patients will be allowed to treat HAE attacks for up to 1 year following the first attack treated with sebetralstat (i.e. for 52 weeks following the first treatment with investigational medicinal product [IMP] for an HAE attack) or until the patient reaches 12 years of age or the trial is completed. Each attack will initially be treated with a single dose of sebetralstat. The estimated duration of this trial for each patient will be up to 1 year from the first attack treated with sebetralstat. The trial will be closed after sufficient data are collected to support regulatory requirements or the last patient completes the trial. The trial will be conducted at HAE treatment centers worldwide on an outpatient basis and will comprise outpatient and televisits. Screening Visit Eligible patients, ages 2 to 11 years old, will undergo a screening assessment for trial inclusion. A parent or legally authorized representative (LAR) must provide signed informed consent, and patients must provide assent (as applicable) as outlined in local regulations, prior to any trial-related procedures being performed. During the Screening Visit, a physical examination, patient weight, laboratory tests (including diagnostic testing for HAE), medical history, prior and concomitant medication review, and other assessments as outlined in the Schedule of Events (Table 1) will be performed. Caregivers must be a parent or other LAR that provides care and management during the treatment of HAE attacks.

	Enrollment Visit Within 8 weeks of the Screening Visit, an Enrollment Visit will occur. The visit will include review of changes to medical history, concomitant medication review, vital sign collection, patient weight, IMP training and dispensing (for 1 HAE attack), and diary training and dispensing. In addition, patients will be dosed with IMP followed by IMP tolerability monitoring and PK sampling; further detail is provided below. <u><i>Tolerability and Pharmacokinetic Assessment</i></u> During the Enrollment Visit, patients will be dosed with IMP and monitored for tolerability. PK samples will be collected via either venous access or capillary collection (e.g. finger prick) at 0.5 hours (± 5 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose. The patient will be monitored for adverse events (AEs) during the collection period, and vital signs will be collected pre-dose and after the final PK sample is collected. The time of the last meal prior to IMP dosing will also be collected. The PK assessments should be completed during the Enrollment Visit but may occur at any other visit; it is not required to complete the PK assessments before the patient takes IMP. Bi-Annual Visits The patient will have Bi-annual Visits every 26 weeks (± 4 weeks), regardless of whether they have treated an HAE attack. Once the patient has treated their first attack with IMP, they may treat their HAE for up to 52 weeks, until their 12th birthday, or until the trial is completed, whichever occurs first. During the Bi-annual Visits, AE review, concomitant medication review, vital sign collection, patient weight, IMP accountability and diary review and collection (as applicable), collection/dispensing of IMP, and retraining (as applicable) will occur. The Bi-annual Visit can be waived if the Attack 1 Visit has occurred within the previous 4 weeks. Attack 1 Visit Within 2 weeks after the first IMP-treated HAE attack, the patient will return to the trial site for an AE review, concomitant medication review, vital sign collection, patient weight, IMP accountability and dispensing, and diary review, collection, dispensing, and retraining (as applicable). Enough IMP and diaries to treat and assess up to 2 HAE attacks will be dispensed. Additional IMP with corresponding diaries may be dispensed if the patient experiences (or is expected to experience) frequent HAE attacks. Post Attack Televisits After each IMP-treated attack, the caregiver will contact the trial staff as soon as possible to review AEs, concomitant medications, ensure IMP dosing compliance, and ensure the diary was completed as required. The site should maintain contact with the caregiver in between bi-annual visits for routine follow-up per normal standard of care and to ensure all IMP-treated attacks have been reported and assessed. IMP Supply Visits Unscheduled visits may occur to perform IMP accountability and resupply. If an unscheduled visit occurs, then diary review, collection, dispensing, and retraining (as applicable) should also occur, in addition to recording patient weight. Enough IMP and diaries to treat and assess up to 2 HAE attacks will be dispensed. Additional IMP with corresponding diaries may be dispensed if the patient experiences (or is expected to experience) frequent HAE attacks.
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Dose Increase Visit

As soon as possible after the implementation of Protocol Version 3.4, patients who are ongoing in the trial should return to the study center for an unscheduled visit to receive IMP at the new dose level. After providing consent/assent as applicable for the new dose level, new IMP will be dispensed. All unused IMP at the patient's previous dose level must be accounted for and returned before the new dose level of IMP can be dispensed. The patient's weight will also be collected at the Dose Increase Visit, and diaries will be reviewed and collected. A Tolerability and Pharmacokinetic Assessment at the new dose level should be conducted as soon as possible after the dose increase. PK samples will be collected via either venous access or capillary collection (e.g. finger prick) at 0.5 hours (± 5 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose. The patient will be monitored for AEs during the collection period, and vital signs will be collected pre-dose and after the final PK sample is collected. The time of the last meal prior to IMP dosing will also be collected.

Final Visit/Early Termination (ET)

The Final/ET Visit will occur after one of the following events (± 2 weeks), whichever occurs first:

- 52 weeks has elapsed since the first treatment with IMP for an HAE attack
- The patient is 12 years old
- The trial has completed

The visit will entail final safety checks including an AE review, concomitant medication review, blood sampling for laboratory safety measurements, vital sign collection, patient weight, final diary review and collection, and final IMP accountability review and collection. Whenever possible, this visit should be completed prior to starting any new medication or treatment.

HAE Attacks Eligibility and Treatment

HAE attacks will be considered eligible for treatment with IMP if at least 48 hours have elapsed since the patient has used conventional on-demand treatment or IMP to treat an HAE attack. Attacks should initially be treated with a single administration of IMP. Patients/caregivers will be encouraged to treat at the earliest recognition of the start of the attack.

A second dose of IMP may be taken 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. Up to 2 doses of IMP can be taken within a 24-hour period. The packaging contains a third dose and this may be taken **at least 24 hours** after the first dose. No more than 3 total doses of IMP may be taken for any attack.

Conventional on-demand treatment may be taken at any time if HAE attack symptoms are considered severe enough by the caregiver/patient to require treatment.

Caregivers or patients with safety or tolerability concerns will be instructed to contact the Investigator or designee as soon as possible or the nearest emergency service as appropriate.

Patient Diary

Caregivers will complete the diary and record the following information through 24 hours as documented in [Table S1](#). All timed diary assessments should be completed except during sleep.

Table S1: Frequency of Diary Assessments

Assessment	Pre-dose	0.5 h, 1.0 h, 1.5 h, and 2 h post-dose	3 h and 4 h post-dose	6 h and 8 h post-dose	12 h, 18 h, and 24 h post-dose	Additional dose of IMP or conventional on-demand treatment ^a
Window	NA	±15 min	±30 min	±1 h	±3 h	
Attack Location	X	X	X	X	X	X
Date/Start time of attack onset	X					
Time of IMP dose(s)	X					X
CaGI-C		X	X	X	X	X
CaGI-S	X	X	X	X	X	X
Caregiver burden	X					
Treatment adherence	X ^b					

Abbreviations: CaGI-C=Caregiver Global Impression of Change; CaGI-S=Caregiver Global Impression of Severity; h=hour; IMP=investigational medicinal product; min=minute; NA=not applicable; ODT = orally disintegrating tablet
^a When additional doses of IMP or conventional on-demand treatment are needed, specified assessments are completed before the patient takes each dose. Assessments then continue through 24 hours from the first dose of IMP.

^b Treatment adherence will be completed after administration of IMP and will ask whether or not the patient fully swallowed the ODT, and if not, the reason for non-adherence.

Investigational Medicinal Product

Sebetralstat orally disintegrating tablet (ODT).

Tablets should be allowed to disintegrate in the mouth before swallowing. If needed, tablets can be added to a beverage (e.g. apple juice) or soft food (e.g. apple sauce or yogurt) to help with administration.

Attacks should be treated with a single administration of IMP at the earliest recognition of the start of the attack. If needed (as determined by the caregiver/patient), up to 3 total doses of IMP may be administered for each attack.

The dose levels for both the 300 mg and 600 mg equivalents were selected using a population-based PK model. The PK of sebetralstat was best described by a 2-compartment model with mixed first and zero-order absorption with absorption lag time on the zero-order process and linear elimination. The model supported interindividual variability on apparent clearance, apparent central volume of distribution, first-order absorption rate constant with a proportional error structure, weight on clearance, and volume using allometric scalars. Weight groups were created and analyzed to determine groupings that best resemble exposures of sebetralstat measured in adults. Results are included in [Table S2](#).

The dose level will be selected by the investigator based on the weight of the patient, as guided by the table below, and as determined appropriate by the investigator. Weight will be measured at every outpatient visit during the trial. If the patient's weight changes during the trial to a different grouping, the dose may be adjusted at the investigator's discretion. The unused IMP will be returned to the site and the new dose will be supplied.

	<table><tr><th colspan="4">Table S2: Dose-Level Assignment</th></tr><tr><th>Weight (kg)</th><th>≥9.5 and <20</th><th>≥20 and ≤45</th><th>>45</th></tr><tr><td>Dose Group (mg)</td><td>150</td><td>300</td><td>600</td></tr></table>	Table S2: Dose-Level Assignment				Weight (kg)	≥9.5 and <20	≥20 and ≤45	>45	Dose Group (mg)	150	300	600
Table S2: Dose-Level Assignment													
Weight (kg)	≥9.5 and <20	≥20 and ≤45	>45										
Dose Group (mg)	150	300	600										
Number of Patients	Up to 48 patients will be enrolled into the trial to ensure sufficient number of patients treated at the intended dose level.												
Population	The trial population will include male and female patients 2 to 11 years of age with a confirmed diagnosis of HAE Type I or II. Inclusion Criteria 1) Male or female patients 2 to 11 years of age. 2) Confirmed diagnosis of HAE Type I or II at any time in the medical history: a) Documented clinical history consistent with HAE (subcutaneous [s.c.] or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND EITHER i) Diagnostic testing results obtained prior to enrollment that confirm HAE Type I or II: complement 1-esterase inhibitor [C1-INH] functional level <40% of the normal level. Patients with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Testing may be obtained from central or local laboratories or obtained from documented historical testing results. Patients may be retested at any time prior to enrollment if results are incongruent with clinical history or believed by the Investigator to be confounded by recent prophylactic or therapeutic C1-INH use, OR ii) Documented historical genetic results, if available, that confirm known mutations for HAE Type I or II. 3) For patients ≥20 kg at screening, patient has had at least 1 documented HAE attack in the last year prior to screening. 4) Caregiver, as assessed by the Investigator, must be able to appropriately store and administer IMP and be able to read, understand, and complete the diary. 5) Investigator believes that the patient and caregiver are willing and able to adhere to all protocol requirements. 6) Parent or LAR provides signed informed consent and patient provides assent (when applicable). Exclusion Criteria 1) Any concomitant diagnosis of another form of chronic angioedema, such as acquired C1 inhibitor deficiency, HAE with normal C1-INH, idiopathic angioedema, or angioedema associated with urticaria. 2) A clinically significant history of poor response to bradykinin receptor 2 blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator. 3) Patient weighs <9.5 kg. 4) Use of angiotensin-converting enzyme inhibitors after the Screening Visit. 5) Any estrogen-containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Screening Visit.												

	6) Patients who require sustained use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers or moderate CYP3A4 inducers. Note: These medications include but are not limited to the following: Inhibitors: boceprevir, clarithromycin, cobicistat, dasabuvir, danoprevir, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole. Inducers: <i>Strong:</i> apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort. <i>Moderate:</i> cenobamate, efavirenz, bosentan, etravirine, phenobarbital, primidone, dabrafenib, lorlatinib, pexidartinib, sotorasib. 7) Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial. 8) Known hypersensitivity to sebetralstat or to any of the excipients. 9) Participation in any interventional investigational clinical trial within 4 weeks of the last dosing of investigational drug prior to the Screening Visit.
Assessments	Safety Variables - Adverse events, including serious adverse events (SAEs). - Trial discontinuations. - Laboratory test results. - Vital signs. Efficacy Variables - Caregiver Global Impression of Change (CaGI-C) scored on a 7-point rating scale as much better, better, a little better, no change, a little worse, worse, much worse. - Caregiver Global Impression of Severity (CaGI-S) scored on a 5-point rating scale as none, mild, moderate, severe, and very severe. - Use of conventional on-demand treatment.
Criteria for Evaluation of Efficacy	- CaGI-C: Time to beginning of symptom relief defined as at least "a little better" (2 time points in a row) within 12 hours of the first IMP administration. - CaGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration. - CaGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration. - Time to use of conventional on-demand treatment within 12 hours of the first IMP administration.
General Statistical Methods and Types of Analyses	No inferential statistical analysis will be performed; the data will be summarized descriptively. Continuous data will be summarized using descriptive statistics (number of observations, arithmetic mean, median, standard deviation, minimum, and maximum). Categorical data will be summarized using frequency tables (frequencies and percentages). All analyses will be carried out using SAS Version 9.4 or higher or using other validated software. Safety analyses will be performed using the Safety Set (SAF). The SAF will include all patients who receive at least 1 dose of IMP.

	Treatment-emergent AEs (TEAEs) and serious AEs (SAEs) recorded during the trial will be summarized by system organ class and preferred term. Adverse events and medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities. The summary will include the number and percentage of patients who experience any TEAE as well as the number of events, TEAEs within 3 days of IMP administration, any SAE, any related TEAE, any severe TEAE, and any related severe TEAE. This summary will also include number of deaths due to a TEAE and number of trial discontinuations due to a TEAE. For physical examinations, vital signs, and laboratory variables (measured by the central laboratory), the number and percentage of patients with normal or abnormal results will be presented at each scheduled visit. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter. The Pharmacokinetic Set (PKS) will include all patients who provide at least 1 PK sample. The PKS will be the population for PK analyses. Plasma concentration time data may be analyzed on an ongoing basis throughout the trial. The Full Analysis Set (FAS) will include all patients who receive at least 1 dose of IMP for a qualifying HAE attack. The FAS will be the population for efficacy analyses. For all IMP-treated attacks, time-to-event efficacy endpoints will be summarized using Kaplan-Meier methods by IMP-treated attack number.
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Table 1: Schedule of Events

Visit	Screening	Enrollment	Bi-Annual Visit	Attack 1 Visit	Post Attack Televisit	IMP Supply Visit	Dose Increase Visit for Protocol V.3.4	ET/ Final Visit
Visit Window	Up to 8 weeks before Enrollment		Every 26 weeks (± 4 weeks)	≤ 2 weeks after first IMP-treated attack	As soon as possible after each IMP-treated attack	Unsched; As needed	Unsched; As soon as possible after V.3.4 approval	After protocol-specified event ^a (± 2 weeks)
Visit Type	Outpatient Visit	Outpatient Visit	Outpatient Visit	Outpatient Visit	Televisit	Outpatient Visit	Outpatient Visit	Outpatient Visit
Informed Consent/Assent	X						X	
Eligibility Assessment	X	X						
Medical History ^b	X	X						
Demographics ^c	X							
Physical Examination	X							
Vital Signs ^d	X	X ^e	X	X			X ^e	X
Weight	X	X	X	X		X	X	X
Laboratory Assessments ^f	X							X
Diary training		X						

- ^b Medical history includes any relevant previous and concurrent diseases, HAE disease history (date of first symptoms of HAE; date of first diagnosis of HAE; HAE attack profile in the past 90 days [location of the attacks; number of the attacks; maximum severity of the attacks]; date of last HAE attack; family history of HAE; most recent C1-INH antigen or functional level as per medical history; most recent C4 level as per medical history) and therapies and supplements taken within the past 90 days, previous participation in interventional clinical trials in the past 30 days.
- ^c Demographics: Date of birth; height (meters [m]); weight (kilograms [kg]); race and ethnicity (if allowed); sex.
- ^d Vital signs include pulse rate, respiration rate, and systolic and diastolic blood pressure. For IMP dosing and PK collection, vital signs should be obtained before IMP administration and after final PK sample is collected.
- ^e Collected prior to IMP dosing and after final PK collection.
- ^f Laboratory assessments performed by a central laboratory; repeat laboratory assessments may be performed by a central or local laboratory. Confirmatory diagnostic testing will be conducted at the Screening Visit only and may be tested centrally or locally (if needed).
- ^g During the Enrollment Visit, patients will be dosed with IMP and monitored for tolerability. PK samples will be collected via either venous access or capillary collection (e.g. finger prick) at 0.5 hours (± 5 min), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose. A sample should be collected even if outside the allowed window. The time of the last meal prior to IMP dosing will also be collected. The PK assessments should be completed during the Enrollment Visit but may occur at any other visit; it is not required to complete the PK assessments before the patient takes IMP. After implementation of amendment v3.4, another PK assessment will be completed for ongoing patients at the increased dose level.
- ^h May occur at any visit.
- ⁱ AEs recorded from the time of first administration of IMP up to and including Final/ET Visit. SAEs are recorded from signing of the informed consent/assent up to and including Final/ET Visit.

4. KEY CONTACT LIST

Sponsor	KalVista Pharmaceuticals Ltd Porton Science Park Bybrook Road Porton Down Salisbury, SP4 0BF United Kingdom [REDACTED] Vice President, Clinical Phone: [REDACTED] Email: [REDACTED]
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Central Laboratory	LabConnect 2304 Silverdale Drive, Suite 100 Johnson City, TN 37601 USA
Medical Monitor	[REDACTED] Associate Medical Director, Medical Department Country Director Lithuania Phone: [REDACTED] Email: [REDACTED]
Pharmacovigilance for SAE Reporting	Arriello Ireland Limited SAE Reporting Email: [REDACTED] SAE Reporting Fax#: [REDACTED] North America: [REDACTED] EMEA, APAC: [REDACTED]
All other contact details are located in trial-specific documentation.	

5. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	angiotensin-converting enzyme
AE	adverse event
AUC _{0-inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinity
BR2	bradykinin receptor 2
C1-INH	complement 1-esterase inhibitor
CaGI-C	Caregiver Global Impression of Change
CaGI-S	Caregiver Global Impression of Severity
CI	confidence interval
CL/F	apparent clearance
C _{max}	maximum concentration
CRO	Contract Research Organization
CYP3A4	cytochrome P450 3A4
DBP	diastolic blood pressure
eCRF	electronic case report form
EC	Ethics Committee
ET	early termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
HAE	hereditary angioedema
HR	heart rate
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
i.v.	intravenous
kg	kilogram(s)

LAR	legally authorized representative
mL	milliliter(s)
ms	millisecond(s)
NOAEL	no-observed adverse effect level
ODT	orally disintegrating tablet
pdC1-INH	plasma derived C1-inhibitor concentrate
PK	pharmacokinetic
PKS	Pharmacokinetic Set
PR	pulse rate
rhC1-INH	recombinant human C1-esterase inhibitor
RR	respiration rate
s	second(s)
SAE	serious adverse event
SBP	systolic blood pressure
s.c.	subcutaneous
SOE	Schedule of Events
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
USM	Urgent Safety Measure
VAS	visual analogue scale
Vd/F	volume of distribution

6. INTRODUCTION

6.1 Background

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

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

HAE is a life-long condition with approximately 50% of patients experiencing their first attack before the age of 10 years (Bork et al. 2006, Nordenfelt et al. 2016) and more than 75% experiencing their first attack before adulthood (Maurer et al. 2019). Attacks are episodic with considerable variations in frequency and severity (Bork et al. 2006, Javaud, Altar et al. 2019). Swelling has been shown to affect subcutaneous (s.c.) 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, ecallantide, a specific inhibitor of plasma kallikrein given subcutaneously to treat attacks of HAE, 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 be effective in the prophylactic treatment of HAE, lowering the rate of attacks in HAE patients compared with placebo, and highlighting the role that plasma kallikrein plays in this disease.

Sebetralstat has been shown in a range of non-clinical experiments to be a selective inhibitor of plasma kallikrein. This activity was confirmed in activated plasma samples from completed trials of sebetralstat in healthy volunteers (KVD900-101) and patients with Type I or II HAE (KVD900-201) at dose levels up to 600 mg. Mean inhibition of plasma kallikrein activity in the activated plasma was maintained above 95% for 3 to 4 hours in both populations. It was therefore a plausible hypothesis that treatment with a single dose of sebetralstat 600 mg may be effective to treat HAE attacks. This hypothesis was tested in a phase 2 trial (KVD900-201) for the on-demand treatment of HAE attacks. The trial was a cross-over in which 53 patients with either Type I or II HAE completed. Results showed a significant difference between 600 mg sebetralstat and placebo for the primary endpoint of time to conventional treatment use and secondary endpoints of attack improvement using Patient Global Impression of Change (PGI-C), Patient Global Impression of Severity (PGI-S), and a composite visual analogue scale (VAS) measuring symptoms of the attack.

The clinical efficacy and safety of 2 dose levels of sebetralstat was investigated in a phase 3 trial (KVD900-301), a double-blind, randomized, placebo-controlled, multicenter, clinical trial in patients 12 years of age or older with HAE Type I or II. Patients were randomized to 6 treatment sequences in a 3-way crossover design. Eligible attacks were treated with placebo, 300 mg, or 600 mg sebetralstat per attack (with the option for patients to take a second dose of IMP to treat each attack) with a minimum 48-hour washout period between attacks. Sebetralstat is also being investigated in an ongoing open-label, multicenter extension trial (KVD900-302) to evaluate the long-term safety of a single dose of 600 mg sebetralstat (with the option for patients to take a second dose of IMP to treat each attack) in patients who are 12 years of age or older with HAE Type I or II. Long-term efficacy is being evaluated as a secondary objective.

There is a clear unmet medical need for oral treatments that pediatric patients are able to administer at the earliest recognition of an attack, thereby reducing the time to treatment which in turn has been shown to improve clinical outcomes. Of particular interest to patients with HAE is a pediatric-specific oral dosage form that does not require injectables. Such a pediatric-focused oral dosage form would be a very useful addition to the clinical armamentarium for the treatment of HAE attacks in pediatric patients aged 2 to 11 years old.

The current trial, KONFIDENT-KID, is an open-label, multicenter clinical trial to investigate the safety, pharmacokinetic (PK), and efficacy of sebetralstat in patients aged 2 to 11 years old with HAE Type I or II. The investigational medicinal product (IMP) used in this trial is sebetralstat orally disintegrating tablets (ODT), which disintegrate in the mouth before swallowing. If needed, tablets may be added to a beverage such as apple juice or soft foods such as apple sauce or yogurt to aid in administration.

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

6.3 Benefit/Risk

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

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

In the completed phase 1 healthy volunteer trials and the phase 2 and 3 trials in patients with Type I or II HAE, single and multiple doses (up to three 600 mg doses within 24 hours) of sebetralstat were well tolerated with no IMP-related serious adverse events (SAEs) and no deaths. Refer to the IB for further detail on sebetralstat.

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

In the double-blind, placebo-controlled phase 3 trial (KVD900-301) in patients 12 years and older with Type I or II HAE, 1 or 2 doses of 300 mg or 600 mg sebetralstat were found to be safe and tolerable with a comparable safety profile to matching placebo control. AEs while on treatment considered by the investigator to be related to the IMP were reported for 2 of 86 patients (2.3%) administered sebetralstat (AEs of dyspepsia and fatigue) and 2 of 93 patients (2.2%) administered sebetralstat 600 mg (AEs of headache and nausea), compared with 4 of 83 patients (4.8%) administered placebo (AEs of dysgeusia, headache, irregular menstruation, nausea, and rash).

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

A completed open-label, single dose, crossover study trial in healthy subjects (KVD900-108) evaluated the comparative bioavailability, safety, and tolerability of a 600 mg film-coated tablet dose compared to a 500 mg ODT dose and compared to a 600 mg ODT dose. Following sebetralstat 600 mg ODTs versus 600 mg film-coated tablets, overall plasma sebetralstat exposure (based on area under the plasma concentration-time curve from time 0 extrapolated to infinity [$AUC_{0-\infty}$]) was slightly higher (90% confidence interval [CI] for $AUC_{0-\infty}$: 103% to 119%) and peak exposure (based on maximum concentration [C_{max}]) was approximately 21% higher (90% CI: 108% to 136%). There were no differences in safety or tolerability between the ODT and film-coated tablets.

The current trial (KVD900-303) has been designed to evaluate the safety and tolerability, PK, and clinical efficacy of sebetralstat in pediatric patients with HAE Type I or II. Each attack will initially be treated with a single ODT dose of sebetralstat. If needed (as determined by the patient and/or caregiver), up to 3 total doses of IMP may be administered for each attack.

The current trial permits the use of HAE prophylactic therapies as detailed in [Section 11.1](#). It is not anticipated that sebetralstat would cause or be affected by drug-drug interactions with these medications. The potential for non-small molecule treatments such as lanadelumab and C1-INH to affect the PK of small molecules such as sebetralstat is generally limited to proinflammatory cytokines or those that cause increases in proinflammatory cytokine levels ([FDA Guidance for Industry, Drug-Drug Interaction Assessment for Therapeutic Proteins, 2023](#)). The non-small molecule prophylactic treatments allowed do not fall into these categories, and therefore it is not anticipated that the PK profile of sebetralstat would be impacted ([European Medicines Agency, Takhzyro \[lanadelumab\] Assessment Report, 2018](#)). Based on available data on berotralstat and KVD900, it is assumed that co-administration with KVD900 would have little to no impact on the PK of berotralstat. Data have shown an increase of 45% and 124% in C_{max} and AUC, respectively, of midazolam (a prototypical cytochrome P450 3A4 [CYP3A4] substrate) with co-administration of berotralstat ([BioCryst Pharmaceuticals, Inc, 2023](#)). KVD900 is not expected to be a more sensitive CYP3A4 substrate than midazolam; therefore, a similar increase in C_{max} and AUC can be assumed. An increase in exposure to this magnitude which would not be a clinically significant increase for KVD900.

Overall, the KONFIDENT-KID trial is considered to have a positive benefit-risk balance given that:

- Inhibition of plasma kallikrein is an established mechanism for the treatment of HAE. There are currently approved plasma kallikrein inhibitors that do not have known target-related AEs.
- Non-clinical studies support the duration of the trial and the dosing regimen, and the inclusion of pediatric population age 2 to 11.
- Sebetralstat was shown to be efficacious and significantly different from placebo in symptom improvement in the PGI-C and PGI-S in patients with Type I or II HAE in the phase 2 clinical trial (KVD900-201) and phase 3 clinical trial (KVD900-301).
- Patients will be monitored for safety findings as indicated in the Schedule of Events (SOE) ([Table 1](#)).

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

7. OBJECTIVES AND ESTIMANDS

7.1 Objectives

7.1.1 Primary Objective

The primary objective of this trial is to evaluate the safety and tolerability of sebetralstat in pediatric patients aged 2 to <12 years of age with HAE Type I or II.

7.1.2 Secondary Objectives

The secondary objectives of this trial are:

- To evaluate the PK of sebetralstat in pediatric patients with HAE Type I or II.
- To evaluate the clinical efficacy of sebetralstat for the on-demand treatment of HAE attacks in pediatric patients with HAE Type I or II.

7.2 Estimands

7.2.1 Primary Estimand

The primary estimand is the proportion of pediatric patients with HAE Types I or II who take any sebetralstat dose, who experience any AE(s) (including fatal AEs) during the study, irrespective of uses of other medications and sebetralstat discontinuations for any reason.

7.2.2 Secondary Estimands

The secondary estimand is the median time to event by sebetralstat-treated attack number for each time-to-event endpoint, in pediatric patients with HAE Types I or II, regardless of prohibited medications and without conventional attack treatment use and as if patients have not discontinued the trial.

8. TRIAL DESIGN

8.1 Overall Design

KVD900-303 (KONFIDENT-KID) is an open-label, multicenter clinical trial in patients aged 2 to 11 years old with HAE Type I or II. The trial will be conducted at HAE treatment centers worldwide on an outpatient basis and will comprise outpatient and televisits. A trial schematic is presented in [Figure 1](#).

Patients will be allowed to treat HAE attacks for up to 1 year following the first attack treated with sebetralstat (i.e. for 52 weeks following the first treatment with IMP for an HAE attack) or until the patient reaches 12 years of age or the trial is completed. Throughout the trial, attacks will initially be treated with a single administration of IMP. HAE attacks will be considered eligible for treatment with the IMP if at least 48 hours have elapsed since the patient has used conventional on-demand treatment or IMP to treat an HAE attack. Patients/caregivers will be encouraged to treat at the earliest recognition of the start of the attack. If needed (as determined by the caregiver/patient), up to 3 total doses of IMP may be administered for each attack. Details on administration of IMP are provided in [Section 10.1](#).

The estimated duration of this trial for each patient will be up to 1 year from the first attack treated with sebetralstat. The trial will be closed after sufficient data are collected to support regulatory requirements or the last patient completes the trial.

Screening Visit

Eligible patients, ages 2 to 11 years old, will undergo a screening assessment for trial inclusion. A parent or legally authorized representative (LAR) must provide signed informed consent, and patients must provide assent (as applicable) as outlined in local regulations, prior to any trial-related procedures being performed.

During the Screening Visit, a physical examination, patient weight, laboratory tests (including diagnostic testing for HAE), medical history, prior and concomitant medication review, and other assessments as outlined in the SOE ([Table 1](#)), will be performed. Site personnel will train patients and caregivers on the use of IMP and the information they will be expected to provide in the diary. Caregivers must be a parent or other LAR that provides care and management during the treatment of HAE attacks.

Enrollment Visit

Within 8 weeks of the Screening Visit, an Enrollment Visit will occur. The visit will include review of changes to medical history, concomitant medication review, vital sign collection, patient weight, IMP training and dispensing (for 1 HAE attack), and diary training and dispensing. In addition, patients will be dosed with IMP followed by IMP tolerability monitoring and PK sampling; further detail is provided below.

Tolerability and Pharmacokinetic Assessment

During the Enrollment Visit, patients will be dosed with IMP and monitored for tolerability. PK samples will be collected via either venous access or capillary collection (e.g. finger prick) at 0.5 hours (± 5 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose. The patient will be monitored for adverse events (AEs) during the collection period and vital signs will be collected pre-dose and after the final PK sample is collected. The time of the last meal prior to IMP dosing will also be collected. The

PK assessments should be completed during the Enrollment Visit but may occur at any other visit; it is not required to complete the PK assessments before the patient takes IMP.

Bi-Annual Visits

Once the patient is enrolled (i.e. completes the Enrollment Visit), they will have Bi-annual Visits every 26 weeks (± 4 weeks), regardless of whether they have treated an HAE attack. Once the patient has treated their first attack with IMP, they may treat their HAE attacks for up to 52 weeks, until their 12th birthday, or until the trial is completed, whichever occurs first. During the Bi-annual Visits, AE review, concomitant medication review, vital sign collection, patient weight, IMP accountability and diary review and collection (as applicable), collection/dispensing of IMP, and retraining (as applicable) will occur. The Bi-annual Visit can be waived if the Attack 1 Visit has occurred within the previous 4 weeks.

Attack 1 Visit

Within 2 weeks after the first IMP-treated HAE attack, the patient will return to the trial site for an AE review, concomitant medication review, vital sign collection, patient weight, IMP accountability and dispensing, and diary review, collection, dispensing, and retraining (as applicable). Enough IMP and diaries to treat and assess up to 2 HAE attacks will be dispensed. Additional IMP with corresponding diaries may be dispensed if the patient experiences (or is expected to experience) frequent HAE attacks.

Post Attack Televisits

After each IMP-treated attack, the caregiver will contact the trial staff as soon as possible to review AEs, concomitant medications, ensure IMP dosing compliance, and ensure the diary was completed as required. The site should maintain contact with the caregiver in between bi-annual visits for routine follow-up per normal standard of care and to ensure all IMP-treated attacks have been reported and assessed.

IMP Supply Visits

Unscheduled visits may occur to perform IMP accountability and resupply. If an unscheduled visit occurs, then diary review, collection, dispensing, and retraining (as applicable) should also occur, in addition to recording patient weight. Enough IMP and diaries to treat and assess up to 2 HAE attacks will be dispensed. Additional IMP with corresponding diaries may be dispensed if the patient experiences (or is expected to experience) frequent HAE attacks.

Dose Increase Visit

As soon as possible after the implementation of Protocol Version 3.4, patients who are ongoing in the trial should return to the study center for an unscheduled visit to receive IMP at the new dose level. After providing consent/assent as applicable for the new dose level, new IMP will be dispensed. All unused IMP at the patient's previous dose level must be accounted for and returned before the new dose level of IMP can be dispensed. The patient's weight will also be collected at the Dose Increase Visit, and diaries will be reviewed and collected. A Tolerability and Pharmacokinetic Assessment at the new dose level should be conducted as soon as possible after the dose increase. The increased dose levels are summarized in [Section 10](#). PK samples will be collected via either venous access or capillary collection

(e.g. finger prick) at 0.5 hours (± 5 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose. The patient will be monitored for AEs during the collection period, and vital signs will be collected pre-dose and after the final PK sample is collected. The time of the last meal prior to IMP dosing will also be collected.

Final Visit/Early Termination

The Final/ET Visit will occur after one of the following events (± 2 weeks), whichever occurs first:

- 52 weeks has elapsed since the first treatment with IMP for an HAE attack.
- The patient is 12 years old.
- The trial has completed.

The visit will entail final safety checks including an AE review, concomitant medication review, blood sampling for laboratory safety measurements, patient weight, final diary review and collection, and final IMP accountability review and collection. Whenever possible, this visit should be completed prior to starting any new medication or treatment.

Patient Diary

Caregivers will complete the diary and record the required information through 24 hours as documented in [Table 3](#). All timed diary assessments should be completed except during sleep.

Throughout the trial, safety and other assessments will be recorded as outlined in the SOE ([Table 1](#)).

A trial diagram is presented in [Figure 1](#).

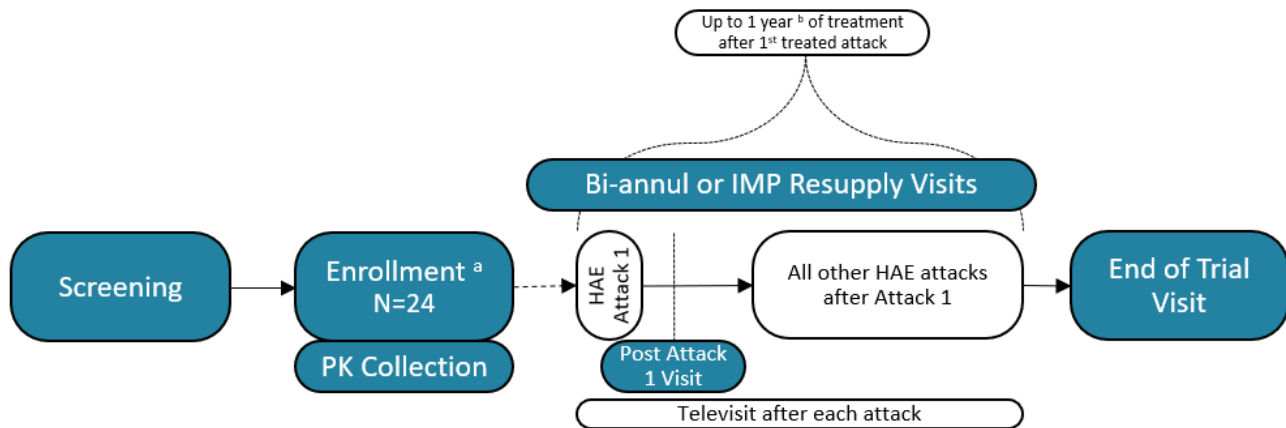


Figure 1: Trial Diagram

^a During the Enrollment Visit, patients will be dosed with IMP and monitored for tolerability. PK samples will be collected via either venous access or capillary collection (e.g. finger prick). The time of the last meal prior to IMP dosing will also be collected. The PK assessments should be completed during the Enrollment Visit but may occur at any other visit; it is not required to complete the PK assessments before the patient takes IMP.

^b Or, until the patient turns 12 years old, or the trial has completed.

8.2 Scientific Rationale for Trial Design

This phase 3 trial will investigate the safety and tolerability, PK, and efficacy of sebetralstat in pediatric patients aged 2 to 11 years old with HAE Type I or II.

Patients are allowed to treat HAE attacks for up to 1 year following the first attack treated with sebetralstat or until they meet stopping criteria. Each attack will initially be treated with a single dose of sebetralstat. If needed (as determined by the patient and/or caregiver), up to 3 total doses of IMP may be administered for each attack.

The open-label extension design is a standard approach for long-term evaluation of safety.

The trial population is representative of the likely target population for the product. Pediatric patients are being evaluated because this is a genetic disorder that impacts both pediatrics and adults; pediatric patients have been included in the trial per global guidelines and standard clinical practice ([Farkas, 2017](#)). The sample size of approximately 12 treated patients is considered appropriate to evaluate the safety, PK, and clinical efficacy of sebetralstat in this population.

Sebetralstat has been well tolerated in previous phase 1, phase 2, and phase 3 clinical trials. Refer to the IB for further detail on sebetralstat.

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

8.3 Justification for Dose

The dose levels for both the 300 mg and 600 mg equivalents planned for use in this trial were selected using a population-based PK model. The PK of sebetralstat was best described by a 2-compartment model with mixed first and zero-order absorption, with absorption lag time on the zero-order process and linear elimination. The model supported interindividual variability on apparent clearance (CL/F), apparent central volume of distribution (V_z/F), first-order absorption rate constant (KA) with a proportional error structure, weight on clearance, and volume using allometric scalars. Weight groups were created and analyzed to determine the groupings that best resemble exposures of sebetralstat measured in adults. The results of this analysis formed the dose-level assignment groupings ([Table 2](#)).

Sebetralstat has been well tolerated in previous phase 1, phase 2, and phase 3 clinical trials. Dose levels were increased for all weight bands to match a 600 mg equivalent, in alignment with the approved FDA labeling for sebetralstat.

8.4 End of Trial Definition

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

9. TRIAL POPULATION

The trial population will include male and female patients 2 to 11 years of age with a confirmed diagnosis of HAE Type I or II.

9.1 Inclusion Criteria

- 1) Male or female patients 2 to 11 years of age.
- 2) Confirmed diagnosis of HAE Type I or II at any time in the medical history:
 - a) Documented clinical history consistent with HAE (s.c. or mucosal, nonpruritic swelling episodes without accompanying urticaria) AND EITHER
 - i) Diagnostic testing results obtained prior to enrollment that confirm HAE Type I or II: C1-INH functional level <40% of the normal level. Patients with functional C1-INH level 40-50% of the normal level may be enrolled if they also have a C4 level below the normal range. Testing may be obtained from central or local laboratories or obtained from documented historical testing results. Patients may be retested at any time prior to enrollment if results are incongruent with clinical history or believed by the Investigator to be confounded by recent prophylactic or therapeutic C1-INH use, OR
 - ii) Documented historical genetic results, if available, that confirm known mutations for HAE Type I or II.
- 3) For patients ≥ 20 kg at screening, patient has had at least 1 documented HAE attack in the last year prior to screening.
- 4) Caregiver, as assessed by the Investigator, must be able to appropriately store and administer IMP and be able to read, understand, and complete the diary.
- 5) Investigator believes that the patient and caregiver are willing and able to adhere to all protocol requirements.
- 6) Parent or LAR provides signed informed consent and patient provides assent (when applicable).

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, idiopathic angioedema, or angioedema associated with urticaria.
- 2) A clinically significant history of poor response to bradykinin receptor 2 (BR2) blocker, C1-INH therapy, or plasma kallikrein inhibitor therapy for the management of HAE, in the opinion of the Investigator.
- 3) Patient weighs <9.5 kg.
- 4) Use of angiotensin-converting enzyme (ACE) inhibitors after the Screening Visit.
- 5) Any estrogen-containing medications with systemic absorption (such as oral contraceptives including ethinylestradiol or hormonal replacement therapy) within 7 days prior to the Screening Visit.

- 6) Patients who require sustained use of strong CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers.
- Note: These medications include but are not limited to the following:
- Inhibitors:** boceprevir, clarithromycin, cobicistat, dasabuvir, danoprevir, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole.
- Inducers:** *Strong:* apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort. *Moderate:* cenobamate, efavirenz, bosentan, etravirine, phenobarbital, primidone, dabrafenib, lorlatinib, pexidartinib, sotorasib.
- 7) Any clinically significant comorbidity or systemic dysfunction, which in the opinion of the Investigator, would jeopardize the safety of the patient by participating in the trial.
- 8) Known hypersensitivity to sebetralstat or to any of the excipients.
- 9) Participation in any interventional investigational clinical trial within 4 weeks of the last dosing of investigational drug prior to the Screening Visit.

10. INVESTIGATIONAL MEDICINAL PRODUCT

The sebetralstat formulation used in this clinical trial is an ODT.

The active ingredient in the ODT is sebetralstat.

The dose levels to be administered in this trial as a single dose are:

- >45 kg patient weight: 600 mg (2 x 300 mg) ODT
- 20 to 45 kg patient weight: 300 mg (1 x 300 mg) ODT
- ≥ 9.5 to <20 kg patient weight: 150 mg (2 x 75 mg) ODT

Tablets should be allowed to disintegrate in the mouth before swallowing. If needed, tablets can be added to a beverage (e.g. apple juice) or soft food (e.g. apple sauce or yogurt) to help with administration.

Further information about sebetralstat ODT can be found in the IB.

10.1 Investigational Medicinal Product Administration

HAE attacks will be considered eligible for treatment with IMP if at least 48 hours have elapsed since the patient has used conventional on-demand treatment or IMP to treat an HAE attack. Attacks should initially be treated with a single administration of IMP. Patients/caregivers will be encouraged to treat at the earliest recognition of the start of the attack.

A second dose may be taken 3 hours after the first dose if response is inadequate, or if symptoms worsen or recur. Up to 2 doses can be taken within a 24-hour period. The packaging contains a third dose and this may be taken **at least 24 hours** after the first dose. No more than 3 total doses of IMP may be taken for any attack.

Conventional on-demand treatment may be taken at any time if HAE attack symptoms are considered severe enough by the caregiver/patient to require treatment.

The dose level will be selected by the investigator based on the weight of the patient, as guided by [Table 2](#), and as determined appropriate by the investigator. Weight will be measured at every outpatient visit during the trial. If the patient's weight changes during the trial to a different grouping, the dose may be adjusted at the investigator's discretion. The unused IMP will be returned to the site and the new dose will be supplied.

Table 2: Dose-Level Assignment

Weight (kg)	≥ 9.5 and <20	≥ 20 and ≤ 45	>45
Dose Group (mg)	150	300	600

Caregivers or patients with safety or tolerability concerns will be instructed to contact the Investigator or designee as soon as possible or the nearest emergency service as appropriate.

10.2 Packaging and Labeling

The investigational product (i.e. sebetralstat) will be packaged and labeled according to current International Council for Harmonisation (ICH) Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and national legal requirements. The IMP will be packaged in appropriately labeled blisters with an aluminum foil lid. The blisters will be set into a paperboard kit.

All unused IMP in its original packaging and the packaging from unused IMP will be returned at the outpatient visits.

10.3 Storage and Drug Accountability

Prior to receipt by the caregiver, IMP will be stored as per the label requirements.

IMP will be dispensed to the caregivers according to the procedures described in the Pharmacy Manual. All supplies of the IMP must be accounted for at the end of the trial. Site personnel will inventory IMP at each visit and at the Final/ET Visit.

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

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

10.4 Trial Medication Compliance

Caregivers/patients will be provided with instructions on IMP administration, dosing, and storage. In addition, confirmation of dosing compliance will be performed during each outpatient visit (via review of unused IMP), and retraining will occur, if necessary.

10.5 Randomization and Blinding

Not applicable; this is an open-label, non-randomized trial.

11. PERMITTED THERAPIES AND PROHIBITED THERAPIES

11.1 Conventional On-Demand Treatment

Conventional on-demand treatment is permitted following IMP intake, provided HAE attack symptoms are judged severe enough to require treatment as per the patient's usual treatment regimen. Time of conventional on-demand treatment use for IMP-treated attacks will be entered in the patient diary ([Table 3](#)).

Attacks that are not treated with IMP may be treated with conventional on-demand treatment per the patient's usual treatment regimen. Conventional on-demand treatments include plasma derived C1-inhibitor concentrate (pdC1-INH) intravenous (i.v.), recombinant human C1-esterase inhibitor (rC1INH) i.v., icatibant s.c., or ecallantide s.c.

11.2 Long-term Prophylactic Treatment

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

- i.v. or s.c. plasma-derived C1-INH
- Lanadelumab
- Anti-fibrinolytics (e.g. tranexamic acid)
- Berotralstat

11.3 Prohibited Therapies

Medications and therapies that preclude a patient from enrolling in the trial are listed in [Section 9.2](#).

The following therapy is NOT permitted throughout the trial (i.e. through the Final/ET Visit):

- Long-term prophylactic therapies for HAE not specified in [Section 11.2](#), including:
 - Attenuated androgens (e.g. stanozolol, danazol, oxandrolone, methyltestosterone, testosterone)
- Other investigational therapies for HAE, on-demand or prophylaxis (e.g. garadacimab, donidalorsen, deucricitabent).
- ACE inhibitors
- Estrogen-containing medications with systemic absorption including:
 - Oral contraceptives including ethinylestradiol or hormonal replacement therapy
- Strong CYP3A4 inhibitors and inducers or moderate CYP3A4 inducers:
 - If use of a CYP3A4 inhibitor or inducer is required for treatment of a medical condition during the trial, IMP use should be discontinued and may not be re-started until 5 half-lives have elapsed since stopping the CYP3A4 inhibitor or inducer. Conventional on-demand treatment may be used while the patient is using the CYP3A4 inhibitor or inducer.

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

Inhibitors: boceprevir, clarithromycin, cobicistat, dasabuvir, danoprevir, elvitegravir, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, and voriconazole

Inducers: *Strong:* apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort. *Moderate:* cenobamate, efavirenz, bosentan, etravirine, phenobarbital, primidone, dabrafenib, lorlatinib, pexidartinib, sotorasib.

Details of all medications, therapies and supplements administered starting from 90 days 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 90 days 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.

12. PATIENT DISCONTINUATION

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

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

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

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

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

Discontinued patients will not be replaced; patient identification numbers of withdrawn patients will not be reused. If a patient does not complete a scheduled visit, every effort should be made to contact the patient to reschedule the visit. All efforts should be documented in the patient's medical source record. Patients may be rescreened with Sponsor approval.

13. ASSESSMENTS

The following assessments will be performed and recorded in the eCRF. The SOE by Visit is displayed in [Table 1](#).

13.1 Patient Demographics and Medical History

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

Medical history will include relevant previous and concurrent diseases, HAE disease history (date of first symptoms of HAE; date of first diagnosis of HAE; HAE attack profile in the past 90 days [location of the attacks; number of the attacks; maximum severity of the attacks]; date of last HAE attack; family history of HAE; most recent C1-INH antigen or functional level as per medical history; most recent C4 level as per medical history), therapies and supplements taken within the past 90 days, and previous participation in interventional clinical trials in the past 30 days.

13.2 Safety Assessments

The primary safety variables in this trial are:

- AEs, including SAEs.
- Trial discontinuations.
- Laboratory test results.
- Vital signs.

Procedures for the measurement of these and other safety variables during the trial are presented in the following sections. Definitions and reporting procedures for AEs and SAEs are described in [Section 14](#).

13.2.1 Physical Examination

A physical examination will be performed by the Investigator or his/her qualified designee 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.

13.2.2 Vital Signs and Weight

Vital signs will be assessed in accordance with the SOE ([Table 1](#)). Vital signs will include blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]; mmHg), pulse rate (PR) (beats per minute), and respiration rate ([RR] breaths per minute).

Weight will be collected at every outpatient visit and will be used by the Investigator to guide dose group ([Table 2](#)).

13.2.3 Clinical Safety Laboratory Assessments

Blood samples will be taken using standard venipuncture techniques. The central laboratory will provide a Laboratory Manual with detailed procedures and volumes. Safety labs will be collected per the SOE

(Table 1) for evaluation of hematology, clinical chemistry, liver enzymes, electrolytes, coagulation, urinalysis, C1 functional level, C1 antigen, and complement C4.

The Investigator must review Screening Visit laboratory results for patient eligibility prior to enrollment. 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. Patients may be rescreened upon Sponsor approval.

Laboratory assessments will be performed by a central laboratory; repeat laboratory assessments may be performed by a central or local laboratory. Confirmatory diagnostic testing will be conducted at the Screening Visit only and may be tested centrally or locally (if needed).

13.3 Pharmacokinetic Assessments

During the Enrollment Visit, enough blood will be collected via either venous access or capillary collection to saturate six 10 µL microsampling absorbent tips (Neoteryx by Trajan) for determination of sebetralstat concentration levels will be collected at the time points specified in the SOE (Table 1). Patients who are ongoing at the time of implementation of protocol amendment v3.4 will also have a PK assessment at their increased dose level. Details regarding PK collection, storage, and shipping information will be provided.

Samples will be shipped to the following facility:

York Bioanalytical Solutions Limited
Cedar House
Northminster Business Park
Hackness Road
Upper Poppleton
York
YO26 6QR
United Kingdom

Validated assays will be used to measure KVD900 from blood samples.

13.4 Efficacy Assessments

Efficacy variables of interest in this trial are:

- Change in overall HAE attack symptoms assessed using the CaGI-C, scored on a 7-point rating scale as much better, better, a little better, no change, a little worse, worse, much worse
 - How would you describe your child's HAE attack symptoms right now, compared with how they were when they took the study medication?
- Overall HAE attack severity assessed on the CaGI-S scored on a 5-point rating scale as none, mild, moderate, severe, very severe
 - How would you rate the severity of your child's HAE attack right now?
- Use of conventional on-demand attack treatment

Caregivers will complete the diary and record the required information through 24 hours as documented in Table 3. All timed diary assessments should be completed except during sleep.

Table 3: Frequency of Diary Assessment

Assessment	Pre-dose	0.5 h, 1.0 h, 1.5 h, and 2 h post-dose	3 h and 4 h post-dose	6 h and 8 h post-dose	12 h, 18 h, and 24 h post-dose	Additional dose of IMP or conventional on-demand treatment ^a
Window	NA	±15 min	±30 min	±1 h	±3 h	
Attack Location	X	X	X	X	X	X
Start of attack	X					
Time of dose	X					X
CaGI-C		X	X	X	X	X
CaGI-S	X	X	X	X	X	X
Caregiver burden	X					
Treatment adherence	X ^b					

Abbreviations: CaGI-C=Caregiver Global Impression of Change; CaGI S=Caregiver Global Impression of Severity; h=hour; IMP=investigational medicinal product; min=minute; NA=not applicable; ODT = orally disintegrating tablet

^a When additional doses of IMP or conventional on-demand treatment are needed, specified assessments are completed before the patient takes each dose. Assessments then continue through 24 hours from the first dose of IMP.

^b Treatment adherence will be completed after administration of IMP and will ask whether or not the patient fully swallowed the ODT, and if not, the reason for non-adherence.

14. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

14.1 Adverse Events

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

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

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

14.2 Serious Adverse Events

Any untoward medical occurrence that at any dose:

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

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

14.3 Time Period and Frequency for Collection

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

14.4 Method of Detection

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

14.5 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient. The assessment of severity is made irrespective of relationship to IMP or seriousness of the event and should be evaluated according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials ([US Department of Health and Human Services, 2007](#)) where possible:

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

14.6 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: Temporal relationship of IMP with the AE, biological plausibility of the drug causing a reaction, dechallenge and rechallenge, 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 historical control group.

14.7 Reporting

14.7.1 Reporting AEs to EC/IRB and Regulatory Authorities

The Investigator is responsible for informing the local Ethics Committee (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.

14.7.2 Reporting Serious Adverse Events or Urgent Safety Measures

Urgent Safety Measures (USMs) are procedures that may be undertaken by the Sponsor or the Investigator to protect a research patient from an immediate hazard to their health or safety. USMs can be implemented without seeking approval from Regulatory Authorities or ECs in the countries where the clinical trial is being conducted.

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

USM and SAE forms are to be submitted to [REDACTED]

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

14.7.3 Reporting Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is an AE that meets all the following criteria:

- Serious: as defined in [Section 14.2](#) of this protocol.
- Unexpected: AE is not consistent with the Reference Safety Information (found in the IB).
- Suspected Adverse Reaction: relationship to IMP is suspected to be related as defined in [Section 14.6](#) of this protocol.

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

14.8 Treatment of Overdose

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

15. TRIAL PROCEDURES

KONFIDENT-KID will be conducted on an outpatient basis and will comprise outpatient and televisits. A televisit can be conducted via a telephone call or via an interactive audio/video system.

Trial procedures are summarized by trial visit in the SOE ([Table 1](#)).

15.1 Screening Visit

Eligible patients, ages 2 to 11 years old, will undergo a screening assessment for trial inclusion. A parent or LAR must provide signed informed consent, and patients must provide assent (as applicable) as outlined in local regulations, prior to any trial-related procedures being performed.

Site personnel will train patients and caregivers on the use of IMP and the information they will be expected to provide in the diary. Caregivers must be a parent or other LAR that provides care and management during the treatment of HAE attacks.

The following activities will be performed during the Screening Visit:

- Parent or LAR provides signed informed consent and patient provides assent (as applicable).
- Eligibility assessment evaluating all results of the screening assessment results against the inclusion and exclusion criteria ([Section 9](#)).
- Full medical history ([Section 13.1](#)), including any relevant previous and concurrent diseases, HAE disease history (date of first symptoms of HAE; date of first diagnosis of HAE; HAE attack profile in the past 90 days [location of the attacks; number of the attacks; maximum severity of the attacks]; date of last HAE attack; family history of HAE; most recent C1-INH antigen or functional level as per medical history; most recent C4 level as per medical history) and therapies and supplements taken within the past 90 days, previous participation in interventional clinical trials in the past 30 days.
- Confirmatory HAE diagnostic testing (or confirmation against documented historical testing results).
- Demographics (date of birth; height [m]; weight [kg]; race and ethnicity [if allowed] sex) ([Section 13.1](#)).
- Physical examination ([Section 13.2.1](#)).
- Vital signs (SBP and DBP, PR, and RR) after patient has been resting for at least 5 minutes ([Section 13.2.2](#)).
- Blood samples for clinical laboratory assessments ([Section 13.2.3](#)).
- Prior and concomitant medication review, including caregiver questions about administering current on-demand medication.

15.2 Enrollment Visit

Within 8 weeks of the Screening Visit, an Enrollment Visit will occur. The following activities will be performed during the Enrollment Visit:

- Eligibility assessment evaluating all results of the screening assessment results against the inclusion and exclusion criteria ([Section 9](#)).
- Review changes to medical history.
- Weight (kg).
- IMP dosing and PK sampling.
 - IMP tolerability monitoring (AE monitoring; pre- and post-dose vital sign collection [(SBP and DBP, PR, and RR; [Section 13.2.2](#)]).
 - PK sampling via either venous access or capillary collection (e.g. finger prick) at 0.5 hours (± 5 min), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose ([Section 13.3](#)).
 - Record time of last meal prior to IMP dosing.
 - Note: the PK assessments should be completed at the Enrollment Visit but may occur at a later time associated with any other visit.
- Review concomitant medications.
- Train and dispense IMP (for 1 HAE attack).
- Train and dispense diary.

Once the patient is enrolled, patients/caregivers will be encouraged to treat attacks at the earliest recognition of the start of the attack ([Section 10.1](#)). HAE attacks will be considered eligible for treatment with IMP if at least 48 hours have elapsed since the patient has used conventional on-demand treatment or IMP to treat an HAE attack. Caregivers will complete timed assessments of HAE attack symptoms 24 hours following IMP intake for each treated HAE attack, including CaGI-C and CaGI-S.

15.3 Treatment Period

15.3.1 Bi-Annual Visit

Once the patient is enrolled (i.e. completes the Enrollment Visit), they will have Bi-annual Visits every 26 weeks (± 4 weeks), regardless of whether they have treated an HAE attack. Once the patient has treated their first attack with IMP, they may treat their HAE attacks for up to 52 weeks, until their 12th birthday, or until the trial is completed, whichever occurs first.

The following activities will be performed during the Bi-annual Visits:

- Vital signs (SBP and DBP, PR, and RR) after patient has been resting for at least 5 minutes ([Section 13.2.2](#)).
- Weight (kg).
- Collect, review, and/or dispense diaries, and retrain as applicable.
- Review IMP accountability and collect, dispense, and/or retrain on use of IMP, as applicable.
- Review concomitant medications.
- Record AEs ([Section 14](#)).

The Bi-annual Visit can be waived if the Attack 1 Visit has occurred within the previous 4 weeks.

15.3.2 Attack 1 Visit

Within 2 weeks after the first IMP-treated HAE attack, the patient will return to the trial site where the following activities will be performed:

- Vital signs (SBP and DBP, PR, and RR) after patient has been resting for at least 5 minutes ([Section 13.2.2](#)).
- Weight (kg).
- Collect, review, and/or dispense diaries, and retrain as applicable.
- Review IMP accountability and collect, dispense, and/or retrain on use of IMP, as applicable.
 - Note: typically, enough IMP and diaries to treat and assess 2 HAE attacks will be dispensed. Additional IMP with corresponding diaries may be dispensed if the patient experiences frequent HAE attacks.
- Review concomitant medications.
- Record AEs ([Section 14](#)).

15.3.3 Post Attack Televisit

After each IMP-treated attack, the caregiver will contact the trial staff to perform the following activities via a televisit:

- Record AEs ([Section 14](#)).
- Review concomitant medications.
- Ensure IMP dosing compliance.
- Ensure the diary was completed as required.

The site should maintain contact with the caregiver in between bi-annual visits for routine follow-up per normal standard of care and to ensure all IMP-treated attacks have been reported and assessed.

15.3.4 IMP Supply Visit

Unscheduled visits may occur to perform IMP accountability and resupply. If an unscheduled visit occurs, then diary review, collection, dispensing, and retraining (as applicable) should also occur, in addition to recording patient weight. Enough IMP and diaries to treat and assess up to 2 HAE attacks will be dispensed. Additional IMP with corresponding diaries may be dispensed if the patient experiences (or is expected to experience) frequent HAE attacks.

15.3.5 Dose Increase Visit

As soon as possible after the implementation of Protocol Version 3.4, patients who are ongoing in the trial should return to the study center for an unscheduled visit to receive IMP at the new dose level. The increased dose levels are summarized in [Section 10](#). After providing consent/assent as applicable for the new dose level, new IMP will be dispensed. All unused IMP at the patient's previous dose level must be accounted for and returned before the new dose level of IMP can be dispensed. The patient's weight will also be collected at the Dose Increase Visit, and diaries will be reviewed and collected. A Tolerability and Pharmacokinetic Assessment at the new dose level should be conducted as soon as possible after the

dose increase. PK samples will be collected via either venous access or capillary collection (e.g. finger prick) at 0.5 hours (± 5 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose. The patient will be monitored for AEs during the collection period, and vital signs will be collected pre-dose and after the final PK sample is collected. The time of the last meal prior to IMP dosing will also be collected.

15.4 Final Visit/Early Termination

The Final/ET Visit will occur after one of the following events (± 2 weeks), whichever occurs first:

- 52 weeks has elapsed since the first treatment with IMP for an HAE attack.
- The patient is 12 years old.
- The trial has completed.

The visit will include the following activities:

- Record AEs ([Section 14](#)).
- Review concomitant medications.
- Vital signs (SBP and DBP, PR, and RR) after patient has been resting for at least 5 minutes ([Section 13.2.2](#)).
- Weight (kg).
- Blood samples for clinical laboratory assessments ([Section 13.2.3](#)).
- Review and collect diaries.
- Review IMP accountability and collect unused IMP.

Whenever possible, the Final/ET Visit should be completed prior to starting any new medication or treatment.

16. STATISTICAL CONSIDERATIONS

16.1 Sample Size Determination

Up to 48 patients will be enrolled into the trial to ensure sufficient number of patients treated at the intended dose level.

The sample size is considered appropriate to evaluate safety, PK, and efficacy in this population. With 36 to 48 pediatric patients exposed to sebetralstat, there is an 84.2% to 91.5% probability of observing at least one event for an AE with an innate AE rate of 5%.

16.2 Populations for Analyses

- Safety Set (SAF) will include all patients who receive at least 1 dose of IMP.
- Pharmacokinetic Set (PKS) will include all patients who provide at least 1 PK sample. The PKS will be the population for PK analyses.
- Full Analysis Set (FAS) will include all enrolled patients who receive at least 1 dose of IMP for a qualifying HAE attack. The FAS population will be the population for efficacy analyses.

16.3 General Considerations

No inferential statistical analysis will be performed; the data will be summarized only descriptively.

Continuous data will be summarized using descriptive statistics (number of observed values, arithmetic mean, median, standard deviation, minimum, and maximum). Categorical data will be summarized using frequency tables (frequencies and percentages).

All analyses will be carried out using SAS Version 9.4 or higher or using other validated software. Further details will be provided in the Statistical Analysis Plan.

16.4 Analysis of Disposition

The number and percentage of patients screened, entering, and completing the trial will be presented. Reasons for withdrawal will be summarized.

16.5 Demographics and Baseline Characteristics

Demographic data, medical history (including HAE history), and concomitant medications will be summarized via descriptive statistics, as appropriate.

16.6 Safety Analyses

Safety analyses will be performed using the SAF.

Treatment-emergent adverse events (TEAEs) and SAEs recorded during the trial will be summarized by system organ class and preferred term. AEs and medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities.

The summary will include the number and percentage of patients who experience any TEAE as well as the number of events, TEAEs within 3 days of IMP administration, any SAE, any related TEAE, any

severe TEAE, and any related severe TEAE. This summary will also include number of deaths due to a TEAE and number of trial discontinuations due to a TEAE.

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

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

All safety analyses will be performed by age group (2 to 5 years and 6 to 11 years) and overall, and by weight group, as defined in dosing groups.

16.7 Pharmacokinetic Analyses

Pharmacokinetics of sebetralstat in the trial population will be evaluated for a descriptive analysis. Plasma concentration-time data may be analyzed on an ongoing basis throughout the trial.

A separate modeling and simulation analysis plan will be prepared, and the results will be described in a separate report from the clinical study report.

16.8 Efficacy Analyses

See [Section 13.4](#) for efficacy assessments.

Efficacy endpoints are as follows:

1. CaGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration.
2. CaGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration.
3. CaGI-S: Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration.
4. Time to use of conventional on-demand treatment within 12 hours of the first IMP administration.

For all IMP-treated attacks, time-to-event efficacy endpoints will be summarized using Kaplan-Meier methods by IMP-treated attack number.

For each patient, the time observed in the trial, the number of HAE attacks experienced, the number of IMP-treated attacks (single-dose and two doses) and the number of attacks treated with conventional on-demand treatment will be described, alongside the characteristics of the attacks (location, severity). This will be summarized for all patients in the FAS.

All efficacy analyses will be performed by age group (2 to 5 years and 6 to 11 years) and overall, and by weight group, as defined in dosing groups.

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

16.9 Interim Analyses

No formal interim analysis are planned.

17. TRIAL ADMINISTRATION

17.1 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.

17.2 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.

Protocol non-compliance will be recorded as protocol deviations throughout the trial. Serious breaches of GCP or of the trial protocol will be reported as required in applicable clinical trial regulations.

17.3 Ethics

17.3.1 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, Regulation (EU) 536/2014, 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.

17.3.2 Informed Consent/Assent

The parent/LAR and the patient (as applicable) will be informed both verbally and in writing about the nature of this trial, the anticipated benefits and risks, the discomfort to which the patient may be exposed, and their right to discontinue their participation at any time of their own free will. Informed consent will be obtained from the parent/LAR and the patient will provide assent (as applicable) according to the regulatory and legal requirements of the participating country. Each prospective parent/LAR and patient (as applicable) will be given a full explanation of the trial, be allowed to read the approved informed consent/assent, and have any questions answered. The authorized person obtaining the informed consent also signs the informed consent/assent. The Investigator will not undertake any investigation specifically required for the clinical trial until valid consent/assent has been obtained. The informed consent/assent forms will be reviewed and approved by the EC/IRB.

17.3.3 Patient Confidentiality

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

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

Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In case of a data security breach, the Sponsor will follow the requirements of local regulations (e.g. General Data Protection Regulation) with respect to notification and reporting of any suspected or actual data breach and will undertake efforts to identify the source of the breach, the nature of data potentially exposed, and the extent of such data exposure, with remedial actions to be implemented based on the type of unauthorized access to trial patient data that may occur. All organizational, contractual, and technical security measures to guarantee the protection of patient privacy will be reassessed in order to mitigate the possible adverse effects.

17.4 Data Handling and Record Keeping

17.4.1 Source Documents

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

17.4.2 Trial Monitoring

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

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

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

17.4.3 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.

17.4.4 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.

17.5 Financing and Insurance

17.5.1 Financial Disclosure

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

17.5.2 Trial Insurance

Clinical trial insurance will be maintained per local regulations.

17.6 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.

17.7 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.

17.8 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.

17.9 Selection of Coordinating Investigator

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

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