

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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STATISTICAL ANALYSIS PLAN

STUDY TITLE:

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

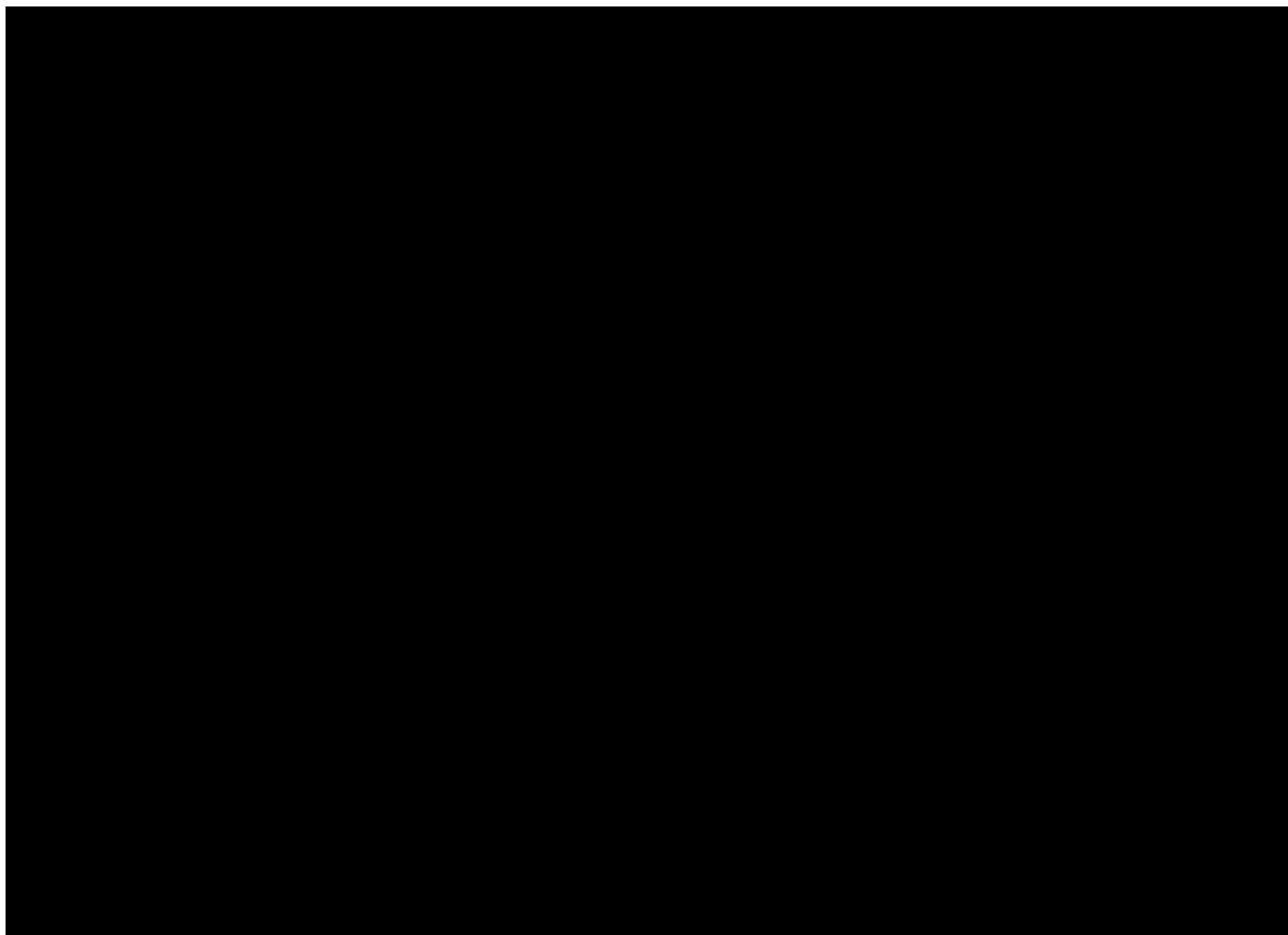
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KVD900-303

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ACKNOWLEDGEMENT AND SIGNATURE SHEET



VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	05 JUN 2025	Finalized version.	
2.0	10 NOV 2025	Summary of changes is presented in SAP Version 2.0	Update following the 3.4 CSP amendment
3.0	23 FEB 2026	Summary of changes is presented below.	Clarify analysis methods

SAP AMENDMENT SUMMARY OF CHANGES

The primary purpose of this amendment is to clarify analysis methods in various places:

- Changed cohort names for Protocol v3.0 (Global) to 300 mg Equivalent Dosing Cohort and Protocol v3.4 (US Only) to 600 mg Equivalent Dosing Cohort
- Added additional demographic variables of country and region ((North America, Europe, Rest of the World)
- Add subgroup variable of country to the summary table of extent of exposure

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

TABLE OF CONTENTS

1.	LIST OF ABBREVIATIONS.....	9
2.	PURPOSE OF THE ANALYSES.....	11
3.	PROTOCOL SUMMARY.....	12
3.1.	Introduction.....	12
3.2.	Study Rationale.....	12
3.3.	Overall Study Design and Plan.....	13
3.4.	Study Objectives.....	15
3.4.1.	Primary Objective and Estimand.....	15
3.4.2.	Secondary Objectives	16
3.5.	Treatments	16
3.6.	Study Population.....	17
3.7.	Sample Size Determination	17
3.8.	Randomization and Blinding	17
4.	ANALYSIS SAMPLES.....	18
4.1.	Analysis Populations	18
5.	GENERAL ANALYSIS AND REPORTING CONSIDERATIONS.....	19
6.	PATIENT DISPOSITION	24
6.1.	Disposition.....	24
6.2.	Protocol Deviations	24
7.	DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS	26
7.1.	Demographics	26
7.2.	Medical History	26
7.2.1.	General Medical History.....	26
7.2.2.	Disease-specific History	26
7.2.3.	Inclusion and Exclusion Criteria	27
7.3.	Treatments and Medications.....	27
7.3.1.	Prior and Concomitant Medications	27
7.3.2.	Study Treatments.....	27
8.	EFFICACY EVALUATION.....	30
8.1.	Efficacy Endpoints.....	30

8.1.1.	CaGI-C: Time to Beginning of Symptom Relief.....	30
8.1.2.	CaGI-S: Time to First Incidence of Decrease from Baseline	31
8.1.3.	CaGI-S: Time to HAE Attacks Resolution.....	32
8.1.4.	Time to First Use of Conventional On-demand Treatment	32
8.1.5.	Summary of HAE Attacks	33
8.2.	Subgroup Analyses	33
9.	SAFETY EVALUATION	34
9.1.	Adverse Events	34
9.1.1.	Relationship of Adverse Events to IMP	34
9.1.2.	Severity of Adverse Event	34
9.1.3.	Serious Adverse Events	35
9.1.4.	Treatment-Emergent Adverse Events.....	35
9.1.5.	Summary of Adverse Events	35
9.2.	Clinical Laboratory Evaluation.....	36
9.2.1.	Hematology.....	37
9.2.2.	Clinical Chemistry and Coagulation.....	37
9.2.3.	Urinalysis.....	37
9.2.4.	Liver Enzymes	37
9.2.5.	C1 Functional Level, C1 Antigen, and Complement C4.....	38
9.3.	Vital Signs, Physical Findings, and Other Observations Related to Safety	38
9.3.1.	Vital Signs	38
9.3.2.	Physical Examinations.....	38
9.3.3.	Pubertal Development Scales	38
10.	PHARMACOKINETIC EVALUATION.....	39
10.1.1.	Plasma Concentration Data.....	39
11.	OTHER ANALYSES	40
12.	INTERIM ANALYSES AND DATA MONITORING	41
13.	REFERENCES	42
14.	APPENDICES	44
14.1.	Study Flow Chart.....	44
14.2.	Schedule of Events – Protocol Version 3.4	45

14.3.	Definitions and Programming Conventions	49
14.3.1.	Algorithms Deriving Time-to-Event Endpoints	49
14.3.2.	Handling of Conventional Medications with Missing Time in Time-to-Event Analyses.....	49
14.3.3.	Handling of Events Achieved after Endpoint Analysis Window	50

LIST OF TABLES

Table 1:	List of Abbreviations	9
Table 2:	Frequency of Diary Assessments.....	15
Table 3:	Protocol-specified Weight Group	19
Table 4:	Definition of Protocol-specified Visits.....	21

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	Body mass index
BUN	blood urea nitrogen
C1-INH	1-esterase inhibitor
CaGI-C	Caregiver Global Impression of Change
CaGI-S	Caregiver Global Impression of Severity
CI	confidence interval
CV%	coefficient of variation
DBP	diastolic blood pressure
eCRF	electronic case report form
ED	Equivalent Dosing
ET	early termination
FAS	Full Analysis Set
Geom CV%	geometric CV%
GGT	Gamma Glutamyl Transferase
HAE	hereditary angioedema
HbA1c	glycosylated hemoglobin
HLGT	high-level group term
HLT	high-level term
HR	heart rate
ICH	International Council for Harmonisation
IMP	investigational medicinal product
kg	kilogram(s)

LAR	legally authorized representative
LLOQ	Lower limit of quantification
LLT	Low-level term
MCH	Mean Corpuscular Hgb
MCHC	Mean Corpuscular Hgb Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
mL	milliliter(s)
NRBC	Nucleated Red Blood Cell
ODT	orally disintegrating tablet
PDS	Pubertal Development Scales
PK	pharmacokinetic
PKS	Pharmacokinetic analysis set
PR	pulse rate
PT	Preferred term
Q1	25 th percentile
Q3	75 th percentile
RBC	Erythrocyte
RDW	Red Cell Distribution Width
SAE	serious adverse event
SAF	Safety analysis set
SBP	systolic blood pressure
SD	Standard deviation
SEM	standard error of the mean
SOC	System organ class
SOE	Schedule of Events
TEAE	treatment-emergent AE
VAS	visual analogue scale
WBC	Leukocytes
WHODrug	World Health Organization drug dictionary

2. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol KVD900-303 (KONFIDENT-KID) Version 1.0 - 3.3 and Version 3.4 (US Only).

This document provides details on study populations, how the variables will be derived, how missing data will be handled and details on statistical methods to be used to analyze the safety and efficacy data.

The SAP is based on International Council for Harmonisation (ICH) guidelines E3 and E9 (Statistical Principles for Clinical Trials).

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Client, and placed on file before database is locked. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Deviations from the final approved plan will be noted in the clinical study report.

3. PROTOCOL SUMMARY

3.1. Introduction

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).

3.2. Study 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.

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. The plausible hypothesis that treatment with a single dose of sebetralstat 600 mg may be effective to treat HAE attacks 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 investigational medicinal product [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.

3.3. Overall Study Design and Plan

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 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. If needed (as determined by the patient and/or caregiver), up to 3 total doses of IMP may be administered for each attack.

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 has been collected to support regulatory requirements or the last patient completes the trial. Up to 48 patients will be enrolled into the trial to ensure sufficient number of patients treated at the intended dose level.

Screening Visit

Eligible patients, ages 2 to 11 years old, will undergo a screening assessment for trial inclusion.

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 (SOE; Section 13.2) will be performed.

Caregivers must be a parent or other legally authorized representative (LAR) that provides care and management during the treatment of HAE attacks.

Enrollment Visit

The enrollment 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 pharmacokinetic (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 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).

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.

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.

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. During the Dose Increase Visit, patient weight, IMP accountability and dispensing, diary review and collection, and new dose level of IMP dispensing will be collected. In addition, as soon as possible after the dose increases, a tolerability and pharmacokinetic assessment at the new dose level will be conducted.

Tolerability and Pharmacokinetic Assessment

During the Dose Increase Visit, patients will be administered with a new dose level of 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 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/Early Termination (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.

Patient Diary

Caregivers will complete the diary and record the following information through 24 hours as documented in Table 2. All timed diary assessments should be completed except during sleep.

Table 2: 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.

A trial diagram is presented in Section 14.1. The schedule of events is presented in Section 14.2.

3.4. Study Objectives

3.4.1. Primary Objective and Estimand

Primary Objective	Estimand Description (Including Endpoint)
To evaluate the safety and tolerability of sebetralstat in pediatric patients aged 2 to <12 years of age with HAE Type I or II.	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.

3.4.2. Secondary Objectives

Secondary Objectives	Estimand Description (Including Endpoint)
To evaluate the pharmacokinetics (PK) of sebetralstat in pediatric patients with HAE Type I or II.	Plasma concentrations of sebetralstat
To evaluate the clinical efficacy of sebetralstat for the on-demand treatment of HAE attacks in pediatric patients with HAE Type I or II.	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.

3.5. Treatments

The sebetralstat formulation used in this clinical trial is an orally disintegrating tablet (ODT).

The dose levels for both the 300 mg equivalent dosing (ED) cohort and 600 mg equivalent dosing (ED) cohort will be selected by the investigator based on the weight of the patient, as follows:

	Weight (kg)		
	≥9.5 to <20	≥20 to ≤45	>45
300 mg ED Cohort	75 mg	150 mg	300 mg
600 mg ED Cohort	150 mg	300 mg	600 mg

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.

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.

For 300 mg ED cohort, additional doses of IMP may be taken for each HAE attack at intervals of at least 3 hours if HAE attack symptoms are considered severe enough by the caregiver/patient to require additional treatment. Up to 3 doses can be taken during a 24-hour period.

For 600 mg ED cohort, 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. A third dose may be taken at least 24 hours after the first dose and 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.

3.6. Study Population

The trial population will include male and female patients 2 to <12 years of age with a confirmed diagnosis of HAE Type I or II.

3.7. 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 a 84.2% to 91.5% probability of observing at least one event for an AE with an innate AE rate of 5%.

3.8. Randomization and Blinding

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

4. ANALYSIS SAMPLES

4.1. Analysis Populations

- Screened Set will include all patients who have signed informed consent.
- Safety Set (SAF) will include all enrolled patients who receive at least 1 dose of IMP.
- Pharmacokinetic Set (PKS) will include all enrolled 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 will be the population for efficacy analyses.

These analysis populations will be applied to each of the corresponding protocol(s) creating three cohorts:

- 300 mg ED cohort: patients consented under protocol v1.0 - v3.3;
- 600 mg ED cohort: patients consented under protocol v3.4 (US Only) only, or under protocol v1.0 - v3.3 and continued to protocol v3.4 (US Only);
- Overall cohort: patients consented under protocols v1.0 - v3.4.

5. GENERAL ANALYSIS AND REPORTING CONSIDERATIONS

All summaries will be presented by the age groups (2 to 5 years and 6 to 11 years) and overall, and by weight group ($\geq 9.5\text{kg}$ and $< 20\text{kg}$, $\geq 20\text{kg}$ and $\leq 45\text{kg}$, $> 45\text{kg}$). All displays, unless stated otherwise, will be produced for each protocol cohort (300 mg ED cohort, 600 mg ED cohort, and Overall). For 300 mg ED cohort, only data before the Dose Increase Visit in Protocol v3.4 (US Only) is included. For 600 mg ED cohort, only data on or after the Dose Increase Visit in Protocol v3.4 (US Only) is included.

For age group presentation, age is defined as the age collected at the Screening Visit. As only year of birth is collected, age is calculated as year of informed consent – year of birth – 1.

The weight measurement used to assign weight group is defined in Table 3, and is used for efficacy, safety, and PK analyses.

Table 3: Protocol-specified Weight Group

	300 mg ED Cohort	600 mg ED Cohort
Efficacy analysis	The last non-missing measurement prior to the first dose of IMP	Patients enrolled under Protocol v3.4 (US Only) only: The last non-missing measurement prior to the first dose of IMP Patients enrolled from Protocol v1.0 - v3.3: The pre-dose measurement at the Dose Increase Visit for Protocol v3.4 (US Only)
Safety/PK analysis	The measurement collected at the Enrollment Visit	Patients enrolled under Protocol v3.4 (US Only) only: The measurement collected at the Enrollment Visit Patients enrolled from Protocol v1.0 - v3.3: The pre-dose measurement collected at the Dose Increase Visit for Protocol v3.4 (US Only)

Continuous data will be presented using descriptive statistics (i.e. n, mean, standard deviation [SD], median, first and third quartiles, minimum, and maximum). Categorical data will be presented using the patient count and percentage in each category. For the summary statistics of all numerical variables (unless otherwise specified), minimum and maximum will be displayed to the same level of precision as the data collected. Mean, median, first and third quartiles will be displayed to one level of precision greater than the data collected. Standard deviation/standard error will be displayed to two levels of precision greater than the data collected. Data will be displayed in all listings sorted by age group and patient number.

Patients will be identified in the listings by a patient identification number.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The

denominator for all percentages will be the number of patients in that group within the analysis set of interest, unless otherwise specified.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to or on the date that the first dose of treatment is taken. Study day is defined in relation to the date of first dose of study drug.

Therefore, when an assessment date is before the first dose:

$$\text{Study day} = \text{assessment date} - \text{first dose date of study drug}$$

and when an assessment is on or after the first dose:

$$\text{Study day} = \text{assessment date} - \text{first dose date of study drug} + 1$$

The protocol-specified visits are defined in Table 4.

Table 4: Definition of Protocol-specified Visits

	Overall	300 mg ED Cohort	600 mg ED Cohort
Baseline	The last non-missing measurement prior to the first dose of IMP (including potential unscheduled visits)	Patients enrolled under Protocol v1.0 - v3.3 only: The last non-missing measurement prior to the first dose of IMP (including potential unscheduled visits) Patients continued to Protocol v3.4 (US Only): The last non-missing measurement prior to the first dose of IMP (including potential unscheduled visits) before Dose Increase Visit	Patients enrolled from Protocol v1.0 - v3.3: The pre-dose measurement at the Dose Increase Visit for Protocol v3.4 (US Only) Patients enrolled under Protocol v3.4 (US Only) only: The last non-missing measurement prior to the first dose of IMP (including potential unscheduled visits)
First IMP Dose Date	The PK dose date or the first IMP-treated attack dose date, whichever occurs the earliest	Patients enrolled under Protocol v1.0 - v3.3 only: The PK dose date or the first IMP-treated attack dose date, whichever occurs the earliest before end of study Patients continued to Protocol v3.4 (US Only): The PK dose date or the first IMP-treated attack dose date, whichever occurs the earliest, before Dose Increase Visit	Patients enrolled from Protocol v1.0 - v3.3: Date of first dose at or after the Dose Increase Visit Patients enrolled under Protocol v3.4 (US Only) only: The PK dose date or the first IMP-treated attack dose date, whichever occurs the earliest before end of study
Last IMP Dose Date	The last IMP dose date before or on study completion	Patients enrolled under Protocol v1.0 - v3.3 only: The last IMP dose date before or on study completion Patients continued to Protocol v3.4 (US Only): The last IMP dose date before or on study completion or before the Dose Increase Visit, whichever occurs the earliest	The latest IMP dose date before or on study completion

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Statistical Analysis Plan - KVD900-303

Final Visit/ End of Study	Study completion	Patients enrolled under Protocol v1.0 - v3.3 only: Study completion Patients continued to Protocol v3.4: Study completion or visit before the Dose Increase Visit, whichever occurs the earliest	Study completion
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For the purpose of inclusion in tables, incomplete start and stop dates (e.g. AEs and prior/concomitant medication) will be imputed as follows:

Missing start dates (where UN and UNK indicate unknown or missing day and month respectively) will be handled as follows:

- UN-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the stop date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the stop date (after any imputation) is prior to the first dose of study drug, then assume the stop date for the start date;
- DD-UNK-YYYY/UN-UNK-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the stop date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the stop date (after any imputation) is prior to the first dose of study drug, then assume the stop date for the start date.

Missing stop dates (where UK and UNK indicate unknown or missing day and month respectively) will be handled as follows:

- UN-MMM-YYYY: Assume the last day of the month
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY
- If a patient dies during the study, the stop date will be imputed as the date of death if the imputed stop date is after date of death.

A month is defined as 28 days. A year is defined as 365.25 days.

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

6. PATIENT DISPOSITION

6.1. Disposition

A listing of screening information (protocol version, date of informed consent, type of consent, parental consent obtained) for all screened patients will be produced.

Patient disposition will be presented for all dosing cohorts (i.e., 300 mg ED cohort, 600 mg ED cohort, and Overall) by age group and overall, and by weight group. The number and percentage of patients screened, failed the screening, all non-met inclusion criteria, all met exclusion criteria, have been included in SAF, FAS, and PKS, and dosed will be presented for all screened patients.

The number and percentage of patients who completed the trial or prematurely discontinued during the trial (and the primary reason) will be presented by age group and overall, and by weight group for all protocol cohorts, using the SAF. Patients are considered to have completed the study if they have met one or more of the following criteria:

- Turned 12 years old before the study ends,
- Participated in the study for 52 weeks (± 2 weeks) since the first treatment with IMP for an HAE attack, or
- Terminated early by the sponsor due to study being closed after sufficient data collection to support regulatory requirements.

If patients do not meet the above completion criteria, they are considered as prematurely discontinued during the trial. Primary reasons for study discontinuation may include any of the following listed reasons:

- Adverse Event
- Death
- Lost to Follow-up
- Non-Compliance with Study Drug
- Physician Decision
- Sponsor Decision
- Withdrawal by Patient
- Other

Patient disposition, patients completing and terminating the trial, and trial analysis sets will be listed by patient for all patients in the Screened Set.

6.2. Protocol Deviations

Protocol deviations will be identified and confirmed prior to database lock and summarized by the deviation categories shown in study deviation rules document. Protocol deviations that might

significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being will be identified as important protocol deviations.

The important protocol deviations will be summarized using the SAF in all protocol cohorts by age group and overall, and by weight group.

Protocol deviations will be listed by site with information such as type of deviation, severity of the deviation (important or non-important), date of occurrence, and protocol deviation description.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1. Demographics

All demographics summaries and listings will be performed using the SAF.

A summary of demographics and baseline information will be presented for all protocol cohorts by age group and overall, and by weight group. The demographic characteristics consist of age (years), sex, race (if allowed), and ethnicity (if allowed). The baseline characteristics consist of height (m; without shoes), weight (kg), weight groups ($\geq 9.5\text{kg}$ and $< 20\text{kg}$, $\geq 20\text{kg}$ and $\leq 45\text{kg}$, $> 45\text{kg}$) at the Enrollment Visit and at prior to the first IMP-treated HAE attack, and body mass index (BMI) (kg/m^2). BMI is calculated as (body weight in kilograms) / (height in meters)².

Age (years), baseline height (m), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of patients by sex (Male, Female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, and Not Reported), race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Unknown, and Other), country, and region (North America, Europe, Rest of the World) will also be reported.

Patient demographic and baseline characteristics, including by-subject FAS membership, will be presented in a listing.

7.2. Medical History

7.2.1. General Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 28.1 or higher. The number and percentage of patients with any medical history will be summarized for each MedDRA coded system organ class (SOC) and preferred term (PT) by age group and overall, and by weight group for all protocol cohorts. Percentages will be calculated based on the number of patients in the SAF.

Patient medical history data including specific details will be presented in a listing.

7.2.2. Disease-specific History

The HAE medical history includes HAE type (Type I or Type II), 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), and family history of HAE.

The number and percentage of patients with each HAE Type (I or II) will be summarized by age group and overall, and by weight group for all protocol cohorts. Percentages will be calculated based on the number of patients in the SAF.

HAE attack history data including specific details described above and start date of last HAE attack prior to screening will be presented in a listing.

7.2.3. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in Sections 9.1 and 9.2 of the protocol. The status of eligibility criteria met, inclusion criteria not met, or exclusion criteria met details will be listed for the screened patients.

7.3. Treatments and Medications

7.3.1. Prior and Concomitant Medications

Information on prior and concomitant medications taken by patients is recorded in the electronic case report form (eCRF). Prior and concomitant medication will be coded according to the latest World Health Organization drug dictionary (WHODRUG) (Version March 2025). Incomplete dates will be imputed according to the rules in Section 5.

All medications will be listed.

7.3.1.1. Prior Medications

Prior medications are defined as those medications taken within 90 days prior to the Screening Visit up to the first dose of IMP.

The total number of prior medications and the number and percentages of patients with at least one prior medication will be summarized. The number and percentages of all prior medications will be summarized by the drug class (Anatomical Therapeutic Chemical [ATC] Class level 3) and preferred term. All summaries will be performed for all protocol cohorts by age group and overall, and by weight group using the SAF.

7.3.1.2. Concomitant Medications

Concomitant medications are defined as those medications ongoing at or started after the first dose of IMP. Information on concomitant medications will be summarized similarly to how prior medications will be summarized for all protocol cohorts by age group and overall, and by weight group using the SAF.

7.3.2. Study Treatments

7.3.2.1. Extent of Exposure

Duration of exposure is defined as the total number of days a patient exposed to study drug and calculated as the total number of days from the first dose date to the end of study (date of last visit – the date of first dose + 1), where the first dose date and end of study for each of the protocol-specified visits are defined in Table 4.

Duration of exposure of the on-treatment period is defined as the total duration of the on-treatment period for PK dosing or each HAE attack.

The on-treatment period for PK dosing or each HAE attack is calculated in the following way:

On-treatment period (in days) = Datetime of the last IMP dose – datetime of the first IMP dose to treat that HAE attack/ PK dosing + 3 days

The first and last dose dates for each of the protocol-specified visits are defined in Table 4.

The duration of exposure to IMP (in weeks) will be summarized for all patients in the SAF and will be presented in a table by summary statistics by country and overall, by age group and overall, and by weight group for all protocol cohorts. The duration of exposure will be classified into the following (cumulative) categories: ≥ 4 weeks, ≥ 12 weeks, ≥ 26 weeks, and ≥ 52 weeks and in these categories 0-3, $\geq 4-11$, $\geq 12-25$, $\geq 26-51$, and ≥ 52 weeks, and will be presented as the number and percentage of patients in each duration category. Percentages will be computed by the number of patients in the SAF.

Additionally, the duration of exposure of the on-treatment period for PK dosing and all HAE attacks (3 days after each IMP used to treat an attack/ PK dosing) will be presented by summary statistics.

A summary of each patient's exposure will be presented in a listing.

Number of HAE attacks experienced, number of IMP-treated attacks (single-dose, two doses, three doses, overall) and number of attacks treated with conventional medication as the initial attack treatment will be summarized.

Number of IMP-treated attacks, IMP-treated attacks categories, and IMP-treated attack frequency (attacks/month) will be summarized, where the duration of exposure to IMP on HAE attacks will be used to calculate the frequency. Additionally, the number of IMP-treated attacks categories include: 1-2 attacks, 3-5 attacks, and >5 attacks; the IMP-treated attack frequency (attacks/month) will be classified into the following categories: 0-0.5 attacks/month, $>0.5-1$ attacks/month, >1 attacks/month.

Number of IMP doses, IMP doses categories, and IMP doses frequency (IMP doses/month) will be summarized. The number of IMP doses categories include: 1-4 doses, 5-10 doses, and >10 doses; the IMP frequency (doses/month) will be classified into the following categories: 0-1, $>1-2$, >2 doses/month.

Categorical summaries will be presented as the number and percentage of patients in each category. IMP-treated attack results will be presented in a listing.

7.3.2.2. Treatment Compliance

For each HAE attack treated with the IMP, treatment compliance is defined as follows:

- 300 mg ED cohort: Attacks treated with 1, 2, or 3 doses will be considered compliant.
- 600 mg ED cohort: Attacks treated with 1 or 2 doses within 24 hours or treated with a 3rd dose at least 24 hours after the first dose will be considered compliant.
- Overall: Attacks compliant under 300 mg ED cohort and compliant under 600 mg ED cohort will be considered compliant.

At the attack level, the number and percentage of IMP-treated HAE attacks with 1, 2, 3, ≥ 4 doses will be presented for all attacks. Moreover, at the patient level, summary statistics on the percentage of compliant HAE attacks for each patient will be presented. Number and percentage of patients in each percent of compliant HAE attacks categories (0 to $< 50\%$, 50% to $< 80\%$, 80% to 100%) will also be presented for all protocol cohorts by age group and overall, and by weight group.

A summary of each patient's compliance will be presented in a listing.

8. EFFICACY EVALUATION

Analysis of efficacy endpoints will be performed by age group and overall, and by weight group for 300 mg ED cohort and 600 mg ED cohort using the FAS.

A qualifying HAE attack is defined as an IMP-treated HAE attack. All efficacy analyses will only include qualifying HAE attacks. Non-qualifying HAE attacks will be presented in a listing, with all available assessments for the attack presented. Analyses in qualifying HAE attacks will be performed in all IMP-treated attacks and by IMP-treated attack number for the attacks that had at least 10 patients.

8.1. Efficacy Endpoints

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 first use of conventional on-demand treatment within 12 hours of the first IMP administration.

8.1.1. CaGI-C: Time to Beginning of Symptom Relief

8.1.1.1. Estimand

Variable: Caregiver Global Impression of Change (CaGI-C) within 12 hours of the first IMP administration.

Population: Pediatric patients aged 2 to <12 years of age with HAE Type I or II.

Intercurrent events: Patients with no events will be right-censored at the end of the analysis window of interest (12 hours after dosing) or at the time of discontinuation, whichever is earlier. Patients treated with conventional medication before reaching the end of the analysis window of interest will be right-censored at 12 hours. If time-to-event results cannot be derived due to a lack of 2 consecutive post-baseline assessments, patients will be censored at time 0. Any other intercurrent events will be ignored for the purposes of analysis.

Population-level summary: The median time for CaGI-C to score at least “a little better” for 2 time points in a row.

8.1.1.2. Analysis Details

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 will be calculated by using:

Time to HAE attack being rated “a little better” or higher for 2 time points in a row (hours) = Datetime of first rating of “a little better” or higher (i.e. better or much better) which is immediately followed by another rating of “a little better” or higher (without missing values in between) – Datetime of first IMP administration.

Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% confidence interval (CI) of time to beginning of symptom relief will be reported. In the case of sparse events not allowing estimation of quantiles, the number and percentage of patients with events will be reported along with summary statistics of the time to first event among those with events.

8.1.2. CaGI-S: Time to First Incidence of Decrease from Baseline

8.1.2.1. Estimand

Variable: Caregiver Global Impression of Severity (CaGI-S) within 12 hours of the first IMP administration.

Population: Pediatric patients aged 2 to <12 years of age with HAE Type I or II.

Intercurrent events: Patients with no events will be right-censored at the end of the analysis window of interest (12 hours after dosing) or at the time of discontinuation, whichever is earlier. Patients treated with conventional medication before reaching the end of the analysis window of interest will be right-censored at 12 hours. If time-to-event results cannot be derived due to a lack of at least 2 post-baseline assessments, patients will be censored at time 0. Any other intercurrent events will be ignored for the purposes of analysis.

Population-level summary: The median time for CaGI-S to decrease from baseline for 2 time points in a row.

8.1.2.2. Analysis Details

Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration will be calculated by using:

Time to First Incidence of Symptoms Decrease from Baseline (hours) = Datetime of first incidence of decrease of symptom intensity from baseline for two time points in a row (with possible missing values in between) – Datetime of first IMP administration.

Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% CI of time to any decrease from baseline will be reported. In the case of sparse events not allowing estimation of quantiles, the number and percentage of patients with events will be reported along with summary statistics of the time to first event among those with events.

8.1.3. CaGI-S: Time to HAE Attacks Resolution

8.1.3.1. Estimand

Variable: Caregiver Global Impression of Severity within 24 hours of the first IMP administration.

Population: Pediatric patients aged 2 to <12 years of age with HAE Type I or II.

Intercurrent events: Patients with no events will be right-censored at the end of the analysis window of interest (24 hours after dosing) or at the time of discontinuation, whichever is earlier. Patients treated with conventional medication before reaching the end of the analysis window of interest will be right-censored at 24 hours. If time-to-event results cannot be derived due to a lack of at least 2 post-baseline assessments, patients will be censored at time 0. Any other intercurrent events will be ignored for the purposes of analysis.

Population-level summary: The median time for HAE attack resolution to be defined as “none” in the CaGI-S.

8.1.3.2. Analysis Details

Time to HAE attack resolution defined as “none” within 24 hours of the first IMP administration will be calculated by using:

Time to HAE attack resolution (hours) = Datetime of first rating of “None” – Datetime of first IMP administration.

Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% CI of time to any decrease from baseline will be reported. In the case of sparse events not allowing estimation of quantiles, the number and percentage of patients with events will be reported along with summary statistics of the time to first event among those with events.

8.1.4. Time to First Use of Conventional On-demand Treatment

8.1.4.1. Estimand

Variable: Elapsed time to first use of conventional on-demand treatment within 12 hours of the first IMP administration.

Population: Pediatric patients aged 2 to <12 years of age with HAE Type I or II.

Intercurrent events: Patients with no events will be right-censored at the end of the analysis window of interest (12 hours after dosing) or at the time of discontinuation, whichever is earlier. Any other intercurrent events will be ignored for the purposes of analysis.

Population-level summary: The median time to first use of conventional on-demand treatment.

8.1.4.2. Analysis Details

Time to first use of conventional on-demand treatment within 12 hours of the first IMP administration will be calculated by using:

Time to first incidence of conventional on-demand attack treatment use (hours) =
Datetime of first incidence of conventional on-demand attack treatment use – Datetime of first IMP administration.

Kaplan-Meier estimates of the 25th percentile (Q1), the median, and the 75th percentile (Q3) and corresponding 95% CI of time to any decrease from baseline will be reported. In the case of sparse events not allowing estimation of quantiles, the number and percentage of patients with events will be reported along with summary statistics of the time to first event among those with events.

8.1.5. Summary of HAE Attacks

The characteristics of the attacks will be summarized by age group and overall, and by weight group for 300 mg ED cohort and 600 mg ED cohort for all patients in the FAS. The HAE attack characteristics consist of baseline CaGI-S severity score, baseline primary attack location, caregiver burden, treatment adherence, and time from attack onset to IMP administration.

The baseline CaGI-S scores will be transformed into numeric values (recoded as 0 (none) to 4 (very severe)) and descriptive statistics (n, mean, SD, minimum, Q1, median, Q3 and maximum) of baseline CaGI-S values will be presented by age group and overall, and by weight group. Additionally, the number and percentage of attacks by baseline CaGI-S category (None, Mild, Moderate, Severe, Very Severe) will be presented by age group and overall, and by weight group.

Summary statistics on the time from onset of attack to first IMP administration will be presented by age group and overall, and by weight group using the FAS. Additionally, the number and percentage of attacks by baseline time to IMP administration category (< 30 minutes, ≥ 30 - < 60 minutes, ≥ 60 minutes) will be reported by age group and overall, and by weight group. Number and percentage of attacks by original baseline primary attack location (Head/Face/Neck, Torso, Arms/Hands, Genitals, Legs/Feet, Abdomen, and Larynx/Throat) and pooled baseline primary attack location (Laryngeal, Abdominal Only, Subcutaneous Only, and Abdominal and Subcutaneous; Mucosal, and Other) will be presented by age group and overall, and by weight group. Baseline characteristics for the IMP-treated attacks will be presented in a listing by age group for all patients in the FAS.

8.2. Subgroup Analyses

All analyses will be performed by age and weight groups. No other subgroup analyses are planned.

9. SAFETY EVALUATION

Unless specified, all safety analyses will be carried out for all protocol cohorts by age group and overall, and by weight group using the SAF.

Safety endpoints include AEs (including SAEs), trial discontinuations, laboratory test results, vital signs, and physical examination findings.

9.1. 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.

Clinical and laboratory AEs will be coded using the current version of the MedDRA (Version 28.1 or higher). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset. HAE attacks will not be considered AEs unless they are considered SAEs.

9.1.1. Relationship of Adverse Events to IMP

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.

In the related TEAE table, if a patient reports multiple occurrences of the same TEAE only the most closely related occurrence will be presented.

Events for which the investigator did not record relationship to IMP will be considered related to IMP for summary purposes. However, by-patient data listings will show the relationship as missing from that captured on the CRF.

9.1.2. Severity of Adverse Event

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.

AEs are graded by the investigator 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) as Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), or Potentially Life-Threatening (Grade 4).

In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe will be presented. The severity grade of events for which the investigator did not record severity will be categorized as “severe” for table summaries and as “missing” in data listings.

9.1.3. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient hospitalization or prolongation, results in significant disability/incapacity, or is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical and scientific judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious AEs (SAEs) are recorded from signing of the informed consent/assent up to and including Final/ET Visit. Any nonserious AEs occurring prior to the first dose of IMP should be recorded as medical history.

9.1.4. Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions, based on the actual AE dates or imputed dates (if partially missing, see Section 4 for imputation rules):

- begins on or after the first dose date of study drug.
- begins before the first dose date of study drug and increases in severity on or after the first dose of study drug.
- is completely missing a start date and the stop date.
- is completely missing a start date and the stop date is on or after the first dose of study drug.

The first dose dates of study drug for each of the protocols are defined in Table 4.

Only TEAEs, those starting or worsening in severity on or after the first dose of study medication, are collected on the eCRF.

For patients consented to Protocol v3.4 (US Only), TEAEs pertain to Protocol v1.0 - v3.3 are defined as TEAEs with a start date before the date of Dose Increase Visit and TEAEs pertain to Protocol v3.4 (US Only) are defined as TEAEs with a start date on or after the date of Dose Increase Visit.

TEAEs can be further classified as on-treatment TEAEs.

An on-treatment TEAE is defined as any TEAE occurring within 3 days post-dose.

For the purpose of inclusion in TEAE tables, Incomplete AE onset and end dates will be imputed as explained in Section 4.

9.1.5. Summary of Adverse Events

The number and percentage of patients with any TEAE, any related TEAE, any TEAE within 3 days of IMP administration, any severe (defined as grade 3 or higher) TEAE, any related severe

TEAE, any serious TEAE, and any related serious TEAE, as well as the total number of events for each category, will be summarized. The number of deaths due to TEAEs, hospitalization due to TEAEs and trial discontinuation due to TEAEs will be presented. The same presentation will be created for on-treatment TEAEs. Both tables will be presented in the SAF.

The number and percentage of patients who experienced at least one TEAE, as well as the total number of TEAEs, will be summarized for all protocol cohorts by age group and overall, and by weight group, by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated using the number of patients in the SAF. TEAEs will be sorted in descending order of frequency of SOC based on the total of all age/weight groups. Within each SOC, PTs will be sorted in alphabetical order of preferred terms.

A tabular overview of AEs will be repeated for the TEAE categories as follows:

- All TEAEs by severity grade
- All TEAEs related to IMP
- All TEAEs related to IMP by severity grade
- All treatment-emergent SAEs
- All on-treatment TEAEs
- All on-treatment TEAEs by severity grade
- All on-treatment TEAEs related to IMP
- All on-treatment TEAEs related to IMP by severity grade
- All on-treatment treatment-emergent SAEs
- All TEAEs leading to trial discontinuation
- All TEAEs leading to death

Percentages will be calculated out of the number of patients in the SAF. Listing will be presented in the SAF. TEAEs and on-treatment TEAEs will be flagged within the listings. A separate display listing will be created for AEs leading to treatment discontinuation and trial discontinuation.

9.2. Clinical Laboratory Evaluation

Laboratory assessments will be performed by a central laboratory; repeat laboratory assessments may be performed by a central or local laboratory. All summaries will be based on the conventional units. Baseline is defined as the last non-missing measurement taken on or prior to the initial IMP administration defined in Table 4.

If laboratory value contains “>”, “=”, “<=”, follow the approach described: if a laboratory value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be added or subtracted to the nearest value based on the number of decimal places of the given numeric value. Example: if the database contains the

value “<0.04”, then for the descriptive statistics the value “0.039” will be used. The value “>100” will be imputed by “100.1”). This new value will be taken where summary tables are presented.

For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline to each scheduled post-baseline visit will be presented by age groups and overall, and by each weight groups. For categorical laboratory results, the number and percentage of patients reporting each result will be presented by age groups and overall, and by weight group.

All relevant clinical laboratory tests will be classified as Low, Normal, and High, or Normal/Abnormal according to the normal ranges. All possible categorical data will be summarized in shift tables comparing the results among all post-baseline visits with those at the baseline visit.

All laboratory data will be presented in a listing on the SAF.

9.2.1. Hematology

The following laboratory tests will be included: WBC (Leukocytes), RBC (Erythrocyte), hemoglobin, hematocrit, platelet count, neutrophils, lymphocytes, monocytes, eosinophils, Basophils, Mean Corpuscular Volume (MCV), Mean Corpuscular Hgb (MCH), Mean Corpuscular HGB Concentration (MCHC), Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV), Nucleated Red Blood Cell (NRBC), Granulocytes. Summary tables and listings will be presented as described in Section 9.2.

9.2.2. Clinical Chemistry and Coagulation

The following clinical chemistry laboratory tests will be included: sodium, potassium, glycosylated hemoglobin (HbA1c), creatinine, glucose (random), triglycerides, blood urea nitrogen (BUN), direct bilirubin, total bilirubin, and total cholesterol.

Coagulation laboratory tests will include INR and PT.

Summary tables and listings will be presented as described in Section 9.2.

9.2.3. Urinalysis

The following laboratory tests will be included: pH, protein, glucose, ketone, bilirubin, blood, nitrite, Leukocytes, urobilinogen, albumin (microalbumin). Summary tables and listings will be presented as described in Section 9.2.

9.2.4. Liver Enzymes

The following laboratory tests will be included: Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyl Transferase (GGT). Summary tables and listings will be presented as described in Section 9.2.

9.2.5. C1 Functional Level, C1 Antigen, and Complement C4

The following laboratory test will be included: C1 esterase inhibitor (C1-INH antigen), C1 esterase inhibitor (functional), and complement C4 results. Summary tables (except the shift from baseline table) and listings will be presented as described in Section 9.2.

9.3. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.3.1. Vital Signs

Summary tables presenting observed values and changes from baseline to each scheduled post-baseline visit will be presented for all protocol cohorts for vital sign data, including systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), pulse rate (PR; bpm), and respiration rate (RR; breaths/minute), by age group and overall, by weight group, for patients in the SAF. The protocol-specified baseline and the final visits are defined in Table 4. All vital sign results will be presented in a listing by age group, patient, and visit using the SAF.

9.3.2. Physical Examinations

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.

A table will summarize physical examination results (complete and brief) for all protocol cohorts by age group and overall, and by weight group, using the SAF. The summary will include number and percentage of patients with each physical examination outcome (Normal; Abnormal).

Physical examination results for all patients will be presented in a listing by age group and patient using the SAF.

9.3.3. Pubertal Development Scales

Pubertal status will be determined using the modified Petersen's Pubertal Development Scales (PDS). The modified PDS is a scale consisting of 1 general question and 2 additional questions specific to the sex of the patient.

The number and percentage of patients of pubertal status (Prepubertal; Early pubertal; Midpubertal; Late pubertal; Post pubertal) will be summarized by age group and overall, and by weight group for 300 mg ED cohort, using the SAF.

PDS results will be listed and sorted by age, weight group, visit, and patient, using the SAF.

10. PHARMACOKINETIC EVALUATION

10.1.1. Plasma Concentration Data

PK samples will be collected for measurement of sebetralstat at 0.5 hours (± 5 min), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post-dose.

Plasma concentrations of sebetralstat will be summarized by age group and overall, and by weight group for 300 mg ED cohort and 600 mg ED cohort, and nominal PK sampling time and listed by patients using the PKS. Summary statistics on the plasma concentrations of sebetralstat will include sample size (n), arithmetic mean (mean), SD, coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, maximum, geometric mean, and geometric CV% (Geom CV%).

Plasma concentrations reported as below the limit of quantification (BLQ) of the assay will be reported as BLQ in the data listings, and BLQ concentrations are treated as 1/2 of LLOQ in the calculation of summary statistics.

Pharmacokinetic parameter analyses will be defined in a PK analysis report.

11. OTHER ANALYSES

Not applicable.

12. INTERIM ANALYSES AND DATA MONITORING

No formal interim analysis are planned.

13. REFERENCES

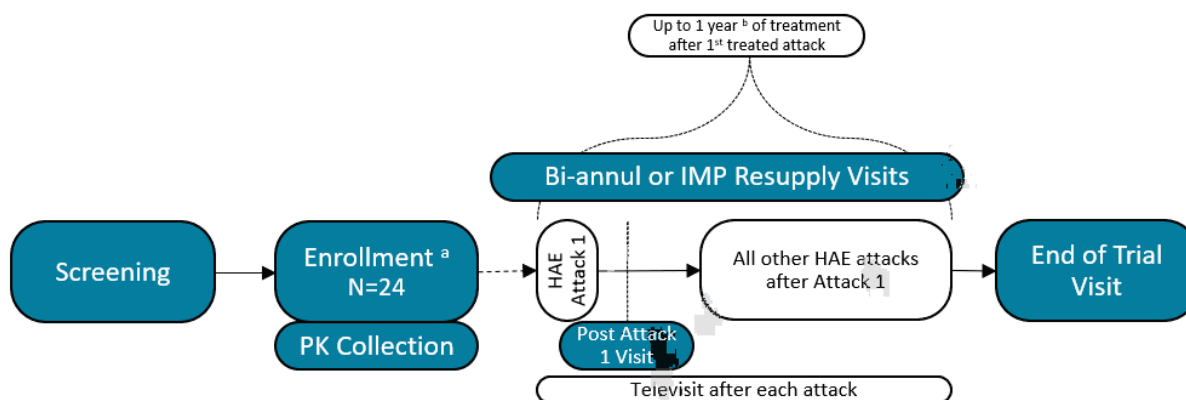
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14. APPENDICES

14.1. Study Flow Chart



14.2. Schedule of Events – Protocol Version 3.4

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	Unscheduled; 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
PDS Questionnaire (to determine pubertal status)	X	X	X					X

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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	Unscheduled; as needed	Unscheduled; 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
Pregnancy Test ^f	X							X
Laboratory Assessments ^g	X							X
Diary training		X						
Diary review, collection, dispensing, and/or retraining		X	X	X	X	X	X	X
IMP accountability/di spensing/ collection		X	X	X		X	X	X
IMP Dosing and PK Collection ^h		X					X ⁱ	
Prior and Concomitant Medications								

KalVista Pharmaceuticals Ltd
Statistical Analysis Plan - KVD900-303

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	Unscheduled; as needed	Unscheduled; 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
Adverse Events ⁱ								

Abbreviations: AE=adverse event; C1-INH=complement 1 esterase inhibitor; ET=early termination; HAE=hereditary angioedema; IMP=investigational medicinal product; PDS= Pubertal Development Scales; PK=pharmacokinetic; SAE=serious adverse event

- ^a The Final/ET Visit will occur after one of the following events (±2 weeks), whichever occurs first: (a) 52 weeks has elapsed since the first treatment with IMP for an HAE attack; (b) the patient is 12 years old; (c) the trial has completed.
- ^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 For female patients who have had their menarche.

^g 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). Volume of blood collected at Screening is approximately 19 mL (including diagnostic testing). Volume of blood collected at ET/Final Visit is approximately 9 mL.

^h 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. Volume of blood collected for PK is up to approximately 2 mL.

- i May occur at any visit.
- j 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

14.3. Definitions and Programming Conventions

14.3.1. Algorithms Deriving Time-to-Event Endpoints

Time-to-event endpoints specified in this SAP encompass symptom assessments, usage of conventional medications, or study discontinuation. This section outlines the algorithms that manage these situations collectively. For time-to event endpoints measuring symptom improvement (e.g., time to beginning of symptom relief, time to first incidence of decrease in PGI-S, etc.), the following algorithm will be followed to determine if an attack met the event or should be censored.

1. First, in the case of derivable time-to-event results, the attack will be treated as achieving the event if the symptom assessments are consistent with the event condition (unless the condition in 2) is met), or right-censored at the end of analysis window if it did not achieve the event.
2. Second, if the attack was treated with conventional attack treatment within the analysis window and prior to the achievement of an event, then the attack will be treated as right-censored at the end of analysis window.
3. Third, in the case of underivable time-to-event results, but a conventional medication was taken within the analysis window, the attack will be right-censored at the end of analysis window.
4. Fourth, in the case of underivable time-to-event results, and no conventional medication was taken within the analysis window, the attack will be censored at 0 hour.
5. Fifth, In the case of discontinuation that prevented event occurrence within the analysis window, the attack will be censored at the time of discontinuation (taken from last assessment done during the end of study visit).

14.3.2. Handling of Conventional Medications with Missing Time in Time-to-Event Analyses

In time-to-event endpoint analyses, unless otherwise specified, time-to-event for an attack with conventional medication use during the analysis window will be right censored at the end of analysis window. In some cases, the time of conventional medication use was missing, while only the date of conventional medication use was available. These cases will be handled conservatively by assuming the conventional medication was used at the end of the analysis window, as reasonable. For example, for an endpoint with a 12-hour analysis window, if the conventional medication with missing time was taken on the same day of the first IMP dosing, or if the conventional medication with missing time was taken on the next day of the first IMP dosing, but the first IMP dosing occurred after 12 pm, then the conventional medication will be considered as occurring at the time point of 12-hour post-dose.

In cases where the occurrence of conventional medication use is the event of interest (e.g. time to first incidence of conventional medication use within 12 hours), instances where the exact timing

of medication usage is missing are treated as if they happened at the end of the analysis window, as reasonable.

14.3.3. Handling of Events Achieved after Endpoint Analysis Window

Actual assessment time will be used in calculating time-to-event results. When a qualifying attack achieves an endpoint at the last assessment time point, this data handling approach may result in a time-to-event that is achieved after the end of the endpoint analysis window (12 or 24 hours depending on the endpoint). For example, an attack may achieve onset of symptom relief at 12.3 hours for an endpoint with a 12-hour assessment window. In order to correctly assess the survival results, time-to-event results in such cases will be set to the end of endpoint analysis window (12 or 24 hours) in summary statistics and statistical modeling. Original time-to-event results will be presented in listings.