***KalVista Pharmaceuticals, Ltd.***

***KVD824-201***

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

***13DEC2022***

Statistical Analysis Plan

**Version 2.00**

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## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AECT | Angioedema Control Test |
| AE-QoL | Angioedema Quality of Life |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate Aminotransferase |
| BID | Twice Daily Dosing |
| BMI | Body Mass Index |
| C1-INH | C1-Esterase Inhibitor |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eDiary | Electronic Diary |
| eGFR | Estimated Glomerular Filtration Rate |
| ET | Early Termination |
| F | Fraction of Non-Missing Data |
| FAS | Full Analysis Set |
| GGT | Gamma Glutamyl Transferase |
| HAE | Hereditary Angioedema |
| IcEV | Intercurrent Event |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| kg | Kilogram(s) |
| LOE | Lack of Efficacy |
| m | Meter(s) |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | Minute(s) |
| mL | Milliliter(s) |
| MNAR | Missing Not at Random |
| MPV | Mean Platelet Volume |
| ms | Millisecond(s) |
| NAcomplete | Complete Number of HAE Attacks |
| NAimputed | Missing Number of HAE Attacks |
| NAobserved | Observed Number of HAE Attacks |
| pH | Potential Hydrogen |
| PPS | Per Protocol Set |
| PT | Preferred Term |
| QoL | Quality-of-Life |
| QTcF | Fridericia Correction of Qtc |
| RBC | Red Blood Cell |

| | |
|---|---|
| RDW | Red Cell Distribution Width |
| s | Second(s) |
| SAE | Serious Adverse Event |
| SAF | Safety Set |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| TSQM | Treatment Satisfaction Questionnaire For Medication |
| WBC | White Blood Cell Differential |
| WHODRUG | World Health Organization Drug Dictionary |

# 1 Introduction

This Statistical Analysis Plan (SAP) defines the statistical methods and data presentations to be used by PPD Biostatistics in the analysis and presentation of data for the KalVista Pharmaceuticals Limited study KVD824-201, entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of Three Dose Levels of KVD824, an Oral Plasma Kallikrein Inhibitor, for Long-Term Prophylactic Treatment of Hereditary Angioedema Type I or II".

Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disease caused by a deficiency in the C1-esterase inhibitor (C1-INH) protein and characterized by unpredictable tissue swelling due to an increase in vascular permeability. 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. 1999, Nussberger et al. 2002).

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

Recurrent swelling in patients with HAE is predominantly a consequence of excessive generation of bradykinin due to dysregulated plasma kallikrein activity (Fields et al. 1983, Nussberger et al. 1998, 2002). Therefore, inhibition of plasma kallikrein activation has emerged as a target for the treatment of HAE. For example, treatment with ecallantide, a specific inhibitor of plasma kallikrein given subcutaneously, led to significantly better treatment outcome scores compared with placebo (Cicardi et al. 2010, Sheffer et al. 2011). The oral small-molecule inhibitor of plasma kallikrein berotralstat (Aygören-Pürsün, Bygum et al. 2018, Zuraw et al. 2020) and the plasma kallikrein monoclonal antibody lanadelumab (Banerji et al. 2017, Banerji et al. 2018) have been shown to lower the rate of attacks in HAE patients compared with placebo, highlighting the role that plasma kallikrein plays in this disease.

This SAP covers all specified analysis for the final study reports based on the following documents:

- Final Protocol, Version 5.0(Amendment 5) , 31 March 2022
- Final Protocol, Version 5.1 for UK only, 04 March 2022
- Final Protocol, Version 5.2 for Canada only, 04 April 2022
- Final Protocol, Version 5.3 for Germany only, 04 April 2022
- Final Protocol, Version 5.4 for Czech Republic only, 04 April 2022
- Electronic Case Report Form (eCRF) Version 6.0 , 17 March 2022

As of 04 October 2022, KalVista issued a press release and announced termination of this study on the observation of liver enzyme elevations in multiple patients. This amendment of the SAP added changes that handle data analyses for this early terminated study.

# 2 Objectives

## 2.1 Primary Objective and Estimand

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

## 2.2 Secondary Objective

Secondary objectives of this trial are:

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

# 3 Investigational Plan

## 3.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 clinical trial to investigate the efficacy and safety of prophylactic treatment with three dose levels of KVD824 in subjects with HAE type I or II. Subjects will be recruited through HAE treatment centers worldwide. This trial will be conducted on an outpatient basis and will comprise in-clinic visits. If in-clinic visits cannot be conducted (e.g. in the event of a pandemic or other reason that prevents the subject from attending the in-clinic visits), home health visits will be used to perform these visits if permitted by the relevant regulatory authority, site's Ethics Committee (EC)/Institutional Review Board (IRB), local regulations, and the subject via informed consent. The home visit will be performed by an appropriately delegated home healthcare service provider. Information captured during a home health visit will mirror that captured in an in-clinic visit.

The Screening Period includes the Screening Visit and Run-in Period. All subjects will sign an Informed Consent Form (ICF) prior to any trial-related procedures being performed. Consent may be collected through a remote e-consenting solution if allowed through country and site regulations. Subjects will be 18 years of age or older at the time of screening and will have a diagnosis of HAE type I or II.

During the visit a physical exam, 12-lead electrocardiogram (ECG), laboratory tests, and other assessments as outlined in the Schedule of Events (Table 3) will also be performed.

Screened subjects will enter a Run-in Period of up to 8 weeks in duration. The start of the Run-in Period is determined by the type of HAE therapy being used by the subject at the time of Screening (one is use of on-demand therapy only for treatment of HAE attacks, and another is use of prophylaxis therapy for treatment of HAE attacks).

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

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

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

The Treatment Period is 12 weeks in duration and starts with the first dose of investigational medicinal product (IMP). Subjects will be instructed to take their first dose with their next morning meal after receipt of the IMP. During the Treatment Period, subjects will self-administer IMP twice daily (BID) (either 300, 600, or 900 mg KVD824, or matching placebo) approximately 12 hours apart with their morning and evening meals in accordance with their randomized assignment. Both the investigator and subject will be blinded to the assigned treatment, but not to the number of tablets assigned (1, 2, or 3).

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

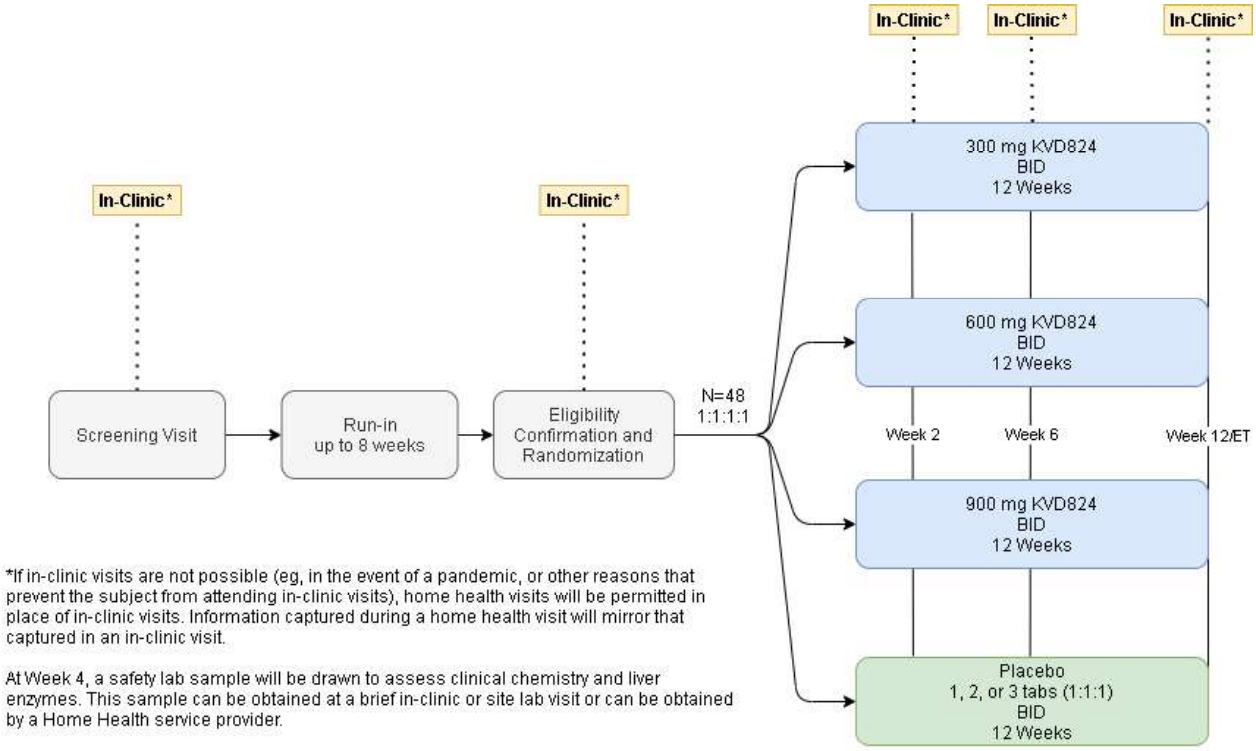
The trial population is representative of the likely target population for the product. The sample size of approximately 48 randomized subjects is required to conclusively evaluate a clinically

relevant treatment effect. A trial duration of 12 weeks is adequate to assess the primary and secondary objectives of the trial and other HAE prophylaxis trials.

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

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

**Figure 1: Trial Diagram***




Additional Country specific visits

| Country | Visit |
|---|---|
| Canada | 1. Post dosing visit (Telephone) |
| Germany | 1. Week 10 visit (In-clinic)<br>2. Post treatment visit (In-clinic) |
| Czech Republic | 1. Week 10 visit (In-clinic*) |

## 3.2 Study Endpoints

### 3.2.1 Primary Endpoint

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

### 3.2.2 Secondary Endpoints

Secondary endpoints of this trial are:

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

### 3.2.3 Exploratory Endpoints

Exploratory endpoints of this trial are:

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

## 3.3 Treatments

KVD824 is a potent and selective small-molecule inhibitor of plasma kallikrein, a major effector in HAE attacks. Orally administered KVD824 achieves sustained and dose-dependent blockade of plasma kallikrein activity. Inhibition of kallikrein is maintained under fed and fasted conditions. KVD824 further protects high molecular weight kininogen from cleavage, thereby blocking the generation of bradykinin.

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

Preclinical investigations, including in-vitro and in-vivo safety pharmacology studies and animal studies in mice, rats, and non-human primates support KVD824 administration in humans. The doses of modified-release KVD824 to be given in this trial were well tolerated in a previous clinical trial comprising 16 subjects who received single doses of KVD824 up to 900 mg and 21 subjects

who received at least 600 mg twice a day for 14 days (Study KVD824-102). All adverse events observed in these studies were of mild and of short duration.

In this study randomized subjects will receive one of the following treatments to be taken BID, 300 mg (1 x 300 mg tablet) KVD824, 600 mg (2 x 300 mg tablets) KVD824, 900 mg (3 x 300 mg tablets) KVD824 or matching placebo.

### 3.4 Dose Adjustment/Modifications

No IMP dose modifications are allowed in this trial. Tablets must be swallowed whole; tablets are not to be crushed or modified in any way. Tablets should be taken approximately 12 hours apart, with the morning and evening meals.

## 4 General Statistical Considerations

The treatment groups will be presented by dose categories (300 mg KVD824 BID, 600 mg KVD824 BID, 900 mg KVD824 BID and Placebo BID). Continuous data will be presented using descriptive statistics (i.e. n, mean, standard deviation, median, first and third quartiles, minimum, and maximum). Categorical data will be presented using the subject 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. 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. P-values will be rounded to four decimal places. If a p-value is less than 0.0001 it will be reported as "<0.0001." If a p-value is greater than 0.9999 it will be reported as ">0.9999." Data will be displayed in all listings sorted by treatment group, and subject number.

Subjects will be identified in the listings by a concatenated subject 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 subjects in that treatment 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:

Study day = assessment date - first dose date of study drug

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

Study day = assessment date - first dose date of study drug + 1

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 UK and UNK indicate unknown or missing day and month respectively) will be handled as follows:

- UK-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/UK-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:

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

If a subject 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.

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).

All statistical tests will be 2-sided with an alpha of 0.05. The primary efficacy endpoint analysis will have Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests will be 2-sided with an alpha of 0.0167. In the outputs, the actual p-values will be presented and a statement describing the adjusted alpha level (0.0167) to which the actual p-values will be compared will be presented in the footnote. The analysis of the secondary or exploratory endpoints will not have multiplicity adjustments.

### 4.1 Sample Size

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

### 4.2 Randomization, Stratification, and Blinding

Subjects will be randomized to double-blinded treatment in a 1:1:1:1 ratio to receive 300 (1 x 300 mg tablet), 600 (2 x 300 mg tablet), or 900 mg (3 x 300 mg tablet) KVD824, or matching placebo. It will be ensured that a balanced number of subjects assigned placebo receive either 1, 2, or 3 tablets. Subjects must not be randomized unless all eligibility criteria have been met.

Randomization will be stratified by the number of investigator-confirmed HAE attacks during the Run-In Period (i.e. ≤3 attacks/4 weeks or >3 attacks/4 weeks).

Subjects, investigators, and site personnel will not be blinded to the number of tablets a subject is assigned (1, 2, or 3 tablets) but will be blinded to the treatment administered until the trial is complete and the database is locked.

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

### 4.3 Intercurrent Events Types

The International Conference on Harmonization E9(R1) guidance (ICH Harmonized Tripartite Guideline) defines intercurrent events (IcEVs) as: "Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated."

Intercurrent event types are displayed in Table 1.

**Table 1: Intercurrent Events Types**

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

| | |
|---|---|
| | a pandemic, personal reasons such as moving from the area, study termination, or the burden of clinic visits). |

### 4.4 Estimand Specifications

Detailed description of all the estimand attributes with the rationale for strategies to address IcEVs are summarized in Table 2.

**Table 2: Estimands Specifications**

| | |
|---|---|
| **Objective** | To demonstrate the clinical efficacy of prophylactic treatment with KVD824 compared with placebo in preventing hereditary angioedema (HAE) attacks. |
| **Estimand Label** | Estimand 1 |
| **Estimand Description** | Rate ratio of Investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo) in subjects with a confirmed diagnosis of HAE type I or II who have at least 1.5 attacks per 4 weeks while off prophylactic treatment.<br><br>Number of attacks will be measured 'while on treatment' over up to 12 weeks or until their treatment stops or changes (expressed as number of attacks on treatment).<br><br>Subjects may receive on-demand conventional care for HAE attacks, but receipt of additional treatments as a prophylactic would constitute a change and the end of that period considered 'while on treatment'. |
| **Target Population** | Subjects with a confirmed diagnosis of HAE type I or II who have at least 1.5 attacks per 4 weeks while off prophylactic treatment and would meet other trial inclusion criteria. |
| **Endpoint** | Rate of Investigator-confirmed HAE attacks during the Treatment Period. |
| **Treatment Conditions** | Twice daily oral self-administration: prophylactic KVD824 doses versus placebo, on top of conventional care including on-demand treatment for an HAE attack. |
| **Population-Level Summary** | Rate ratio of HAE attacks while on treatment (each of the KVD824 dose groups versus placebo). |
| **Intercurrent Event Strategy** | |
| IcV1 (Death) | While on treatment. |
| IcEV2 (Discontinue TEAE) | While on treatment. |
| IcEV3 (Discontinue LOE) | While on treatment. |
| IcEV4 (Prohibited medications) | While on treatment. |
| IcEV5 (Treatment change) | While on treatment. |
| IcEV6 (Discontinue logistical) | While on treatment. |
| **Rationale for Strategies** | The primary focus of this phase 2 trial is to evaluate the attack rate over a period while on assigned treatment prior to the occurrence |

| | |
|---|---|
| | of intercurrent events without use of prohibited medications or additional prophylactic treatments. In the case of an unacceptable level of attacks or tolerability issues resulting in changes to treatment, the measurement period ends. |

### 4.5 Analysis Set

The following analysis population sets will be used in this study:

- Screened Set,
- Enrolled set
- Randomized Set,
- Safety Set,
- Full Analysis Set,
- Per-protocol Set.

#### 4.5.1 Screened Set

The Screened Set includes all subject who have signed informed consent.

#### 4.5.2 Enrolled Set

The Enrolled Set includes all subjects who have signed informed consent and begun the Run-In Period.

#### 4.5.3 Randomized Set

The Randomized Set includes all subjects who are randomized.

#### 4.5.4 Safety Set

The Safety Set (SAF) will include all subjects who are randomized and receive at least one dose of IMP. Subjects will be analyzed according to the actual treatment received.

#### 4.5.5 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who are randomized and receive at least one dose of IMP. Subjects will be analyzed according to randomized treatment. The FAS population will be the population for efficacy analyses.

#### 4.5.6 Per-protocol Set

The Per-protocol Set (PPS) includes all subjects from the FAS who complete at least 28 days of dosing and who do not have pre-defined major protocol deviations that may affect primary efficacy endpoint.

## 5 Subject Disposition

### 5.1 Disposition

A listing of randomization information (including date of informed consent, date of randomization, strata, planned treatment, actual treatment, planned kit, actual kit, randomization and kit number) for all enrolled subjects will be produced.

Subject disposition will be presented for all subjects by treatment group and overall. The number and percentage of subjects who failed the screen (and reason), failed inclusion criteria 6a or 6b, completed run-in, have been randomized and included in Randomized Set, SAF, FAS, and PPS will be presented for all screened subjects.

Discontinued subjects will not be replaced; subject/randomization numbers will not be reused.

If a subject does not complete a scheduled visit, the Investigator will be instructed to use every effort to reschedule the visit. A subject will be considered lost to follow-up if subject cannot be reached after 4 weeks from the scheduled visit.

The number and percentage of subjects who prematurely discontinued during the trial (and the primary reason) will be presented for each treatment group and overall, for SAF. Primary reasons for study discontinuation may include any of the following listed reasons:

- Adverse Event
- Death
- Protocol Violation
- Lost to Follow-up
- Physician Decision
- Pregnancy
- Screen Failure
- Withdrawal by Subject
- Study Termination by Sponsor
- Other

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

### 5.2 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 are considered biasing primary endpoint outcome will be identified as major protocol deviations and will lead to subject exclusion from PP Set.

The major protocol deviations will be summarized by treatment and overall, for all patients in the Randomized Set.

A by-patient listing of protocol deviations will also be presented by treatment group. A flag (Y/N) will be added to the listing to denote whether a patient has a major protocol deviation, and whether a patient is included or excluded from the PPS.

# 6 Demographics and Baseline Characteristics

## 6.1 Demographics

A summary of demographics and baseline information will be presented by treatment group and overall. The demographic characteristics consist of age (years), sex, ethnicity, and race. The baseline characteristics consist of height (m), weight (kg), and body mass index (BMI) (kg/m²). Body mass index is calculated as (body weight in kilograms) / (height in meters)$^2$.

Age (years), baseline height (m), baseline weight (kg), and baseline BMI (kg/m²) will be summarized using descriptive statistics. The number and percentage of subjects by sex (Male, Female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, and Not Reported) and race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, and Other), will also be reported.

Subject demographic and baseline characteristics will be presented in a listing. All summaries and listings will be performed by treatment group using the safety set (SAF) and subject in full analysis set (FAS) will be marked.

## 6.2 Baseline Disease Characteristics

Baseline attack rates per 4 weeks (based on the number of attacks that occurred during the Run-in Period is derived within the EDC system using the equations below). The data obtained from the EDC system will be summarized by treatment group and overall for the SAF and FAS.

For subjects only taking on-demand therapy the equation is:

*4-week attack rate= {(Number of IC-HAE [1]attacks from start of run-in to randomization /Duration of run-in period (from AE-QoL to date of randomization, days)}*28.*

For subjects on prophylactic therapy prior to entering Run-in the equation is:

*4-week attack rate={(Number of IC-HAE[2] attacks from start of run-in to randomization-1 /Duration of run-in period (from completion of 1st IC-HAE[2] attack to date of randomization, days)}*28.*

In addition, attack rate from Run-in to first dose date will also be calculated and summarized using the date of first dose of IMP instead of randomization date in the above formulas.

## 6.3 Medical History

### 6.3.1 General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. The number and percentage of subjects with any medical history will be summarized by treatment group and overall and for each body system. Body systems will be

[1] IC-HAE is investigator confirmed HAE.

included as recorded on the eCRF. Percentages will be calculated based on number of subjects in the SAF and FAS.

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

#### 6.3.2 Disease-specific History

HAE attack history will be collected at the Screening Visit. The HAE attack history includes HAE attack type, relative type (primary and secondary relative) and about current treatment regimen (prophylaxis and on-demand, only).

The number and percentage of subjects with any HAE attack history will be summarized by treatment group and overall and for each HAE type, relative type, and treatment regimen. Percentages will be calculated based on number of subjects in the SAF and FAS.

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

### 6.4 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 using the Enrolled Set.

## 7 Treatments and Medications

### 7.1 Prior and Concomitant Medications

Information on prior and concomitant medications taken by patients are recorded in the eCRF. Prior and concomitant medication will be coded according to the latest World Health Organization drug dictionary (WHODRUG). Incomplete dates will be imputed following rules in Section 4. All medications will be listed.

#### 7.1.1 Prior Medications

Prior medications are defined as those medications taken before the first dose of IMP. Medications taken during the run-in period will be identified separately. Medication taken from the date of entering the run-in period to the day before randomization date will be identified as run-in period medications. Any medications and treatments taken prior to and not stopped prior to the first IMP will be counted in both prior and concomitant medication. The total number of prior medications and the number and percentages of patients with at least 1 prior medication will be summarized. The number and percentages of all prior medications will be summarized by drug class and preferred term. All summaries will be performed by treatment group and overall using the SAF and FAS.

#### 7.1.2 Concomitant Medications

Concomitant medications are defined as those medications (including conventional HAE 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 using the SAF and FAS.

## 7.2 Study Treatments

### 7.2.1 Extent of Exposure

Duration of exposure is defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + 1) as recorded on the Drug Accountability page on the eCRF. If the last dose date on Drug Accountability page is missing, or if a subject is lost to follow-up, but the drug accountability log confirms that the subject has taken study drug, the visit date following the last completed drug accountability log will be used. The duration of exposure to study drug by treatment will be summarized for all subjects in the Safety Set and will be presented in a table by summary statistics. The duration of exposure will be classified into the following (cumulative) categories ≥0 weeks, ≥2 weeks, ≥4 weeks, ≥6 weeks, ≥8 weeks, ≥10 weeks, and will be presented as the number and percentage of subjects in each duration category. Percentages will be computed from the number of subjects in the SAF.

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

### 7.2.2 Treatment Compliance and Modifications

Study drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of study drug as instructed. The number of tablets taken will be calculated by subtracting the number of tablets returned from the number of tablets dispensed.

The overall study drug compliance (%) will be calculated by dividing the total number of tablets taken at all visits by the total number of tablets prescribed for all visits and then multiplying by 100. Compliance (%) = [(total no. of tablets dispensed – total no. of tablets returned) / (Duration of treatment in days *Number of tablets prescribed per day)] * 100.

The overall study drug compliance will be summarized by treatment group and overall.

A subject is considered compliant if overall study drug compliance is greater than or equal to 90% and less than or equal to 100%. A categorical summary of whether subjects were compliant (yes/no) will be presented.

Summary statistics on percentage of treatment compliance as well as the number and percentage of subjects in each compliance category (<90%, 90% to <95%, 95% to <100%, 100% to <105% , 105% to ≤110% and greater than 110% compliant) will be presented overall and by visit. Percentages will be calculated out of the number of subjects who were dosed at that dosing period in the SAF.

No IMP dose modifications are allowed in this trial.

# 8 Efficacy Analysis

Analysis of efficacy endpoints will be performed using the FAS.

All statistical tests will be 2-sided with an alpha of 0.05 unless otherwise is specified.

## 8.1 Primary Efficacy Endpoint

The primary endpoint is the rate of investigator-confirmed HAE attacks during the Treatment Period.

Rate ratio of investigator-confirmed HAE attacks while on treatment (each of the KVD824 dose groups versus placebo) in subjects with a confirmed diagnosis of HAE type I or II who have a baseline of at least 1.5 attacks per 4 weeks while off prophylactic treatment will be analyzed.

The number of attacks will be measured 'while on treatment' over up to 12 weeks or until their treatment stops or changes. Subjects may receive on-demand conventional care for HAE attacks but receipt of additional treatments as a prophylactic would constitute a change and the end of the period considered 'while on treatment'.

Data after occurrence of intercurrent events will not be utilized.

### 8.1.1 Primary Analysis

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

The primary efficacy endpoint analysis will have Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests will be 2-sided with an alpha of 0.0167.

Each active treatment group will be compared to the placebo group with respect to the rate of investigator-confirmed HAE attacks 'while on treatment' using a negative binomial regression model with run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, treatment as a fixed factor and the logarithm of time each subject was observed 'while on treatment' will be used as an offset variable in the model. The 'while on treatment' is defined as day 1 of dosing to the day before additional prophylactic treatment is used or until termination from the IMP due to intercurrent event (see section 4.3). Day 1 is the first date the study drug is taken following randomization. This model will be used to estimate the rates of HAE attacks while on treatment and rate ratios of HAE attacks (each of the KVD824 dose groups versus placebo) with 95% confidence interval and 2-sided p-value that will be reported.

In the case of excessive zeroes in the HAE data, we will use zero-inflated negative binomial model.

All information related to HAE attacks from the eCRF data will be presented in a listing of the FAS.

### 8.1.2 Assumption Testing

Negative binomial models are used when data are over-dispersed. So, this method assumes the conditional variance of the outcome variable to be greater than its conditional mean. To confirm the overdispersion, we will present the residual plot to understand the overdispersion.

### 8.1.3 Supplementary Analysis

A supplementary analysis will be performed handling intercurrent events accordingly to a treatment policy strategy except for the use of additional prophylactic treatment and early

termination from the study treatment. In this analysis, the number of attacks will be measured over up to study/early termination visit or until their use of additional prophylactic treatment. Consistently, time each subject was observed is defined as day 1 of dosing to the day before additional prophylactic treatment is used or until study/early termination visit. All other intercurrent events will be handled using treatment policy strategy. The same analysis method as described in Section 8.1.1 will be performed for this analysis.

### 8.1.4 Other Analysis

Same analysis described in primary analysis (Section 8.1.1) will be conducted using the PPS.

## 8.2 Secondary Efficacy Endpoints

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

The proportion of subjects without investigator-confirmed HAE attacks during the Treatment Period will be analyzed using logistic regression, with treatment as fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable in the model. The number of subjects without investigator-confirmed HAE attacks, and percentages, odds ratios with 95% CI and p-values comparing each dose arm with the placebo arm will be presented. In case of complete or quasi-complete separation in the data, Firth's bias correction will be used to achieve convergence of the logistic regression.

The rate of investigator-confirmed HAE attacks that require conventional treatment during the Treatment Period will be analyzed using negative binomial regression, similar to the primary analysis. The estimated HAE attack rates, rate ratios with 95% CI and p-values will be presented.

The AE-QoL total score and domain scores (see Appendix 15.2 for scoring algorithm), based on 17 items in 4 domains: functioning, fatigue/mood, fears/shame and food, AECT score (see Appendix 15.3 for scoring algorithm) based on 4 questions during the Treatment Period will be summarized. The number and percentage of subjects with an AECT score $\geq 12$ at the end of the Treatment Period will also be reported by treatment group.

The AE-QoL total score and domain scores, and AECT score during the Treatment Period will be analyzed using analysis of covariance (ANCOVA), with treatment group as main effect and run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates. The outcome variable is change of the scores from baseline to the end of treatment. Descriptive summaries of the AE-QoL total score and AECT score (observed and change from baseline) will be presented by treatment and overall. Lsmeans, Lsmeans difference from placebo with 95 % CI and p-values comparing each of the active dose arms with the placebo arm will be presented.

The proportion of subjects with an AECT score $\geq 12$ at the end of the Treatment Period will be analyzed using logistic regression, with treatment as fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable in the model. The estimated proportions, odds ratios with 95% CI and p-values comparing each active dose arm with the placebo arm will be presented. In case of complete or quasi-complete separation in the data, Firth's bias correction will be used to achieve convergence of the logistic regression.

The baseline value for the secondary endpoints will be defined as the most recent non-missing measurement collected prior to the first dose of IMP.

The AE-QOL total score and domain score, AECT score will appear in listings of the FAS.

### 8.3 Exploratory Efficacy Endpoints

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

The rate of investigator-confirmed HAE attacks during the Treatment Period by severity will be analyzed using negative binomial regression model similar to the primary analysis by fitting separate models for each severity level. The estimated HAE attack rates, rate ratios with 95% CI and p-values will be presented separately for each severity level.

The rate of conventional treatment used during the Treatment Period, generated from the eDiary data, will be analyzed using negative binomial regression, similar to the primary analysis, with baseline attack rate as fixed covariate. The estimated HAE attack rates, rate ratios with 95% CI and p-values will be presented.

For each investigator-confirmed HAE attack, time from the most recent IMP dosing to the start of the attack will be derived. Histogram graphs will be produced on time from the most recent IMP dosing to the start of the attack for each treatment group.

The TSQM total and domain scores (see Appendix 15.4 for scoring algorithm) at the end of the Treatment Period will be analyzed using ANCOVA with treatment group as main effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable. A descriptive summary of the TSQM total and domain scores (observed) will be presented by treatment and overall. Lsmeans, Lsmeans difference from placebo with 95 % CI and p-values comparing each of the active dose arms with the placebo arm will be presented.

The TSQM total score will appear in a listing for FAS.

## 9 Safety Analysis

Safety analyses will be performed by treatment group using the SAF and will be presented for actual treatments. Safety endpoints include AEs, clinical laboratory assessments, vital signs, ECG, and physical examination findings.

### 9.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and regardless of its causal relationship to study drug.

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.

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

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (Version 24.0 or higher).

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

Number and percentage of subjects with any AE, SAE, TEAE, serious TEAEs, study drug-related TEAEs, study drug-related serious TEAEs, TEAE leading to study discontinuation, TEAE leading to treatment discontinuation, and AE leading to death will be provided by treatment group and overall. Percentages will be calculated using number of subjects in the Safety Set.

All AEs will be presented in a listing using the Safety Set.

### 9.1.1 Incidence of Adverse Events

Summaries of the number and percentage of subjects with at least one TEAE and the total number of TEAEs will be provided by treatment group and overall. Treatment-emergent AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated using number of subjects in the Safety set.

TEAEs will be sorted in descending order of frequency of SOC based on the total of all treatment groups. Within each SOC, PTs will be sorted in alphabetical order of preferred terms.

### 9.1.2 Relationship of Adverse Events to Study Drug

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Related: A reasonable possibility exists that the IMP caused the AE”, and “Not Related: A reasonable possibility does not exist that the IMP cause the AE”.

A summary of TEAEs by relationship (i.e. “Related” and “Not Related”) to study drug will be presented in a table by incidence of occurrence. In the TEAE relationship table, if a subject reports multiple occurrences of the same TEAE only the most closely related occurrence will be presented. Treatment–emergent AEs that are missing a relationship will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of subjects in the Safety set.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

### 9.1.3 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 subject.

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are "Mild: Grade 1", "Moderate: Grade 2", "Severe: Grade 3", and "Potentially Life-Threatening: Grade 4". In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables as "Severe" but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the Safety set.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

### 9.1.4 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, is a congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability/incapacity.

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

Serious treatment-emergent adverse events (SAEs) will be presented in a table by treatment group and overall. Treatment-emergent SAEs by relationship to study drug will be presented in a table.

A treatment-related treatment-emergent SAE is a treatment-emergent SAE with relationship to study drug as "Related: A reasonable possibility exists that the IMP caused the AE". Treatment-emergent SAEs that are missing a relationship will be presented in the table as "Related" but will be presented in the data listing with a missing relationship. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety set.

The treatment-emergent SAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

### 9.1.5 Adverse Events Leading to Treatment Discontinuation

A summary of TEAEs where the answer to "Action Taken" is "Drug Withdrawn" will be presented in a table by treatment group and overall. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated using number of subjects in the Safety set.

The TEAEs where the answer to "Action Taken" is "Drug Withdrawn" will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

### 9.1.6 Adverse Events Leading to Study Discontinuation

A summary of TEAEs where the answer to "Caused Study Discontinuation" is "Yes" will be presented in a table by treatment group and overall. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety set within the subgroup category.

The TEAEs where the answer to "Caused Study Discontinuation" is "Yes" will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

### 9.1.7 Death

A summary of AEs where the answer to "Outcome" is "Death Related to Adverse Event" will be presented in a table by treatment and overall. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety set.

The summary of AEs where the answer to "Outcome" is "Death Related to Adverse Event" will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

All subjects who have an AE with an outcome of "Death Related to Adverse Event" will be presented in a listing.

## 9.2 Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the conventional units.

Summary tables will be presented for clinical laboratory tests with numeric values by treatment group and overall for subjects in the Safety set. Observed results at each visit will be presented.

Summary tables presenting observed values and changes from baseline will be presented for clinical laboratory tests with numeric values by treatment group for subjects in the Safety set. Changes from baseline to each scheduled post-baseline visit will be presented.

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 at worst result observed among all post-baseline visits with those at the baseline visit. In case of Low and High categories in multiple visits for a subject in a parameter, this subject will consider as "Low & High" category at worst post-baseline side. Missing result will be considered under "Missing" category. All data will be presented in a listing on the Safety Set.

### 9.2.1 Hematology

The following laboratory tests will be included: Red Blood Cell (RBC), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Platelet Volume (MPV), Red Cell Distribution Width (RDW) , nucleated RBC, White Blood Cell Differential (WBC), neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, granulocytes, hemoglobin, and hematocrit. Summary tables and listings will be presented as described in Section 9.2.

### 9.2.2 Clinical Chemistry

The following laboratory tests will be included: glycosylated hemoglobin, creatinine, glucose (random), triglycerides, eGFR, blood urea nitrogen, direct bilirubin, and total cholesterol. 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, and albumin. 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.

Additionally, liver enzyme results will be classified according to the reference ranges. The number of subjects with a non-missing result, and the number and percentage of subjects with a liver enzyme result below the lower limit of normal, within the normal range, and above 3x upper limit of normal, will be summarized by visit for each treatment group for subjects in the Safety set.

#### 9.2.5 Electrolytes

The following laboratory tests will be included: sodium and potassium. Summary tables and listings will be presented as described in Section 9.2.

#### 9.2.6 Coagulation

The following laboratory test will be included: INR. Summary tables and listings will be presented as described in Section 9.2.

#### 9.2.7 C1 Functional Level

The following laboratory test will be included: C1 esterase inhibitor activity. Summary tables and listings will be presented as described in Section 9.2.

#### 9.2.8 C1 Antigen

The following laboratory test will be included where available: C1 esterase inhibitor protein. Summary tables and listings will be presented as described in Section 9.2.

#### 9.2.9 Complement C4

The following laboratory test will be included where available: complement C4. Summary tables and listings will be presented as described in Section 9.2.

#### 9.2.10 Pregnancy

Serum pregnancy tests will be performed on females of childbearing potential. The following laboratory test will be included: human chorionic gonadotropin qualitative. Pregnancy test results will be presented in a listing as described in Section 9.2.

### 9.3 Vital Sign Measurements

Summary tables presenting observed values and changes from baseline to each scheduled post-baseline will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), and respiration (breaths/minute), by treatment group and overall for subjects in the Safety Set.

All vital sign results will be presented in a listing by treatment group, subject, and visit using the Safety Set.

## 9.4 Physical Examination

A physical examination will be performed by the investigator or his/her qualified designee according to the Schedule of Events (Appendix 15.1). A complete physical examination will be performed at Screening only and will include the following body systems: general appearance; ears, nose, and throat; head and neck; ophthalmological; respiratory; cardiovascular; abdomen; neurological; extremities; dermatological; lymphatic; and other. Other visits noted in the Schedule of Events (Appendix 15.1) will include a symptom-directed physical examination.

A table will summarize physical examination results (complete and brief) by treatment group and overall for the Safety set. The summary will include number and percentage of subjects with each physical examination outcome (Normal, Abnormal [Not Clinically Significant, Clinically Significant], Not Done)**.**

Physical examination results for all subjects will be presented in a listing by treatment group, subject and visit using the Safety Set.

## 9.5 Electrocardiogram

All patients will have a standard 12-lead electrocardiogram (ECG) performed at the time points as scheduled (Appendix 15.1), that will be recorded in triplicate readings.

Summary tables presenting observed values and changes from baseline to each scheduled post-baseline visits will be presented for electrocardiogram data, including heart rate (HR; beats per minute), PR-interval (milliseconds [ms]), QRS-duration (ms), QT-interval (ms) and RR interval (milliseconds [ms]), and QTcF (Fridericia correction of QTc; ms) by treatment group and overall for subjects in the Safety Set. Normal sinus rhythm (yes/no) will be presented with number and percentage of subjects by treatment group and visit using the Safety Set.

A table will summarize ECG interpretations by visit for the Safety Set. Interpretation results include Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Not Done.

A shift table comparing the worst interpretation (with worst of all being Abnormal Clinically Significant and best being Normal) observed among all post-baseline visits with those at baseline will be presented using the Safety Set.

All ECG results and interpretation will be presented in a listing by treatment group, subject and visit using the Safety Set.

## 9.6 Other Safety Data

### 9.6.1 Covid-19 Missed Visits or Assessments

All Covid-19 missed visits, missed assessments, and related data will be presented in a listing using the Safety Set.

## 10 Pharmacokinetics

This part is not applicable for this study.

## 11 Pharmacodynamics

This part is not applicable for this study.

## 12 Interim Analysis

This part is not applicable for this study.

## 13 Changes in the Planned Analysis

As of 04 October 2022, KalVista issued a press release and announced termination of this study on the observation of liver enzyme elevations in multiple patients. This amendment of the SAP added changes that handle data analyses for this early terminated study:

- Per Protocol set definition updated.
- Protocol deviations presentation updated.
- Removal of subgroup analyses.
- Primary analysis updated.
- Replacement of sensitivity analysis by a supplementary analysis.
- Use of "run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable" instead of "randomization stratification factor of baseline attack rate per 4 weeks during run-in period as a fixed covariate" in all inferential analyses.
- Histogram graphs on time from the most recent IMP dosing to the start of the attack added.
- Presentation of liver enzymes parameters which are >3x upper limit of normal added.
- Removal of COVID 19 table.
- If the logistic regression calculations of the primary analysis fails to converge, Firth's bias correction will be used.

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# 15 Appendices

## 15.1 Schedule of Events

**Table 3: Schedule of Events**

| | Screening Period[a] | | Randomization Visit | | Treatment Period[b] | | |
|---|---|---|---|---|---|---|---|
| Visit | Screening Visit | Run-In Period (up to 8 weeks prior to Randomization) | | Week 2 | Week 4 | Week 6 | Week 12/ET |
| In-clinic or Home Health Visit[c] | X | | X | X | | X | X |
| Informed Consent[d] | X | | | | | | |
| Eligibility Assessment | X | | X | | | | |
| HAE Diagnostic Lab Test[e] | X | | | | | | |
| Medical History[f] | X | | | | | | |
| Demographics[g] | X | | | | | | |
| Physical Examination[h] | X | | X | | | | X |
| Vital Signs[i] | X | | X | X | | X | X |
| 12-lead ECG[j] | X | | X | X | | X | X |
| Safety Laboratory[k] | X | | X | X | X | X | X |
| Pregnancy Test[l] | X | | X | X | | X | X |
| Subject eDiary Training | X | | | | | | |
| Randomize to Treatment (prior to or during Randomization Visit) | | | X | | | | |
| Subject eDiary Re-training (if necessary) | | | X | X | | X | |

**Table 3: Schedule of Events**

| | Screening Period[a] | | Randomization Visit | | Treatment Period[b] | | |
|---|---|---|---|---|---|---|---|
| Visit | Screening Visit | Run-In Period (up to 8 weeks prior to Randomization) | | Week 2 | Week 4 | Week 6 | Week 12/ET |
| IMP Dispensing/ Accountability/Return[m] | | | X | X | | X | X |
| IMP Dosing | | | | | BID dosing for up to 12 weeks | | |
| HAE Attack Site Follow-up[n] | | ← | ——— | ——— | ——— | ——— | → |
| AE-QOL and AECT Questionnaires[o] | X | | | ← | ——— | → | |
| TSQM | | | | | | | X |
| Prior and Concomitant Medication Review | | ← | ——— | ——— | ——— | ——— | → |
| Adverse Event Review[p] | | | | | ← | ——— | → |

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

a. Procedures for the Screening Visit may take place on different days; however, all procedures must be completed within 4 weeks of starting the visit. For prophylactic subjects, the Run-in Period must start within 8 weeks from completion of Screening Visit eDiary assessments.
b. The start of the Treatment Period begins with the first dose of IMP with the morning meal after the IMP is received; visits for Week 2 and Week 6 should occur within ±3 days. Week 12/ET should occur within 7 days after the last dose of IMP.
c. If a subject cannot attend a trial in-clinic visit (scheduled or unscheduled), a visit at the subject's home is permitted to occur, if permitted by the relevant regulatory authority, site's EC/IRB, local regulations, and the subject via informed consent. The home visit will be performed by an appropriately delegated home healthcare service provider. Information captured during a home health visit will mirror that captured during an in-clinic visit. The home health visits will only occur in the event of a pandemic or other reason that prevents the subject from attending the in-clinic visits.
d. Consent may be collected through a e-consenting solution if allowed through country and site regulations.
e. Diagnostic testing must be performed for subjects without genetic confirmation of HAE Type I or II.

f. Medical history includes any relevant previous and concurrent diseases, HAE disease history; therapies and supplements taken within the past 4 weeks; and previous participation in interventional clinical studies in the past 4 weeks.
g. Demographics: year of birth; height (meters [m]; without shoes); weight (kilograms [kg]); race and ethnicity (if allowed); and sex.
h. Complete physical examination at screening only, all others will be symptom directed. In the case of a home health visit, the home healthcare nurse will conduct an abbreviated physical examination, and the Investigator will conduct the symptom-directed physical examination via televisit.
i. Vital signs include pulse rate, respiratory rate, and systolic and diastolic blood pressure after subject has been resting for at least 5 minutes.
j. ECG to be recorded after subject has rested supine for at least 5 minutes.
k. Laboratory assessments performed by a central laboratory; repeat laboratory assessments may be performed.
l. Serum pregnancy test will be performed on females of childbearing potential.
m. During the Randomization visit, arrangements will be made to dispense the assigned IMP. The IMP will be shipped directly to the subject via a courier service or dispensed at the study clinic as required by local requirements or per the site's local practice, as described in the pharmacy manual. IMP accountability will be performed at the Week 2, 6, and 12/ET visits. Drug accountability will be reviewed at each in-clinic or home health visit (via review of unused IMP), and re-training will occur, if necessary. All unused IMP will be returned at the in-clinic Week 12/ET Visit. If the Week 12/ET Visit is performed by Home Health, arrangements will be made to return any unused IMP via courier.
n. As soon as possible following the completion of each attack and within no more than 5 working days, contact will be made between the site staff and the subject to confirm, clarify, and correct any recorded eDiary data. Site staff who collect the HAE attack information from the subject must be designated and qualified to perform this task. Additionally, the designated site staff will ask questions about each attack to assist the Investigator (or qualified designee) with their confirmation of each attack. The Investigator (or qualified designee) will rate the severity of each attack.
o. AE-QOL and AECT Questionnaires will be collected in the eDiary at the Screening Visit, 4 and 8 weeks post initial dose, and with the last dose of IMP.
p. Adverse events recorded from the first dose of KVD824 or placebo up to and including the Week 12/ET Visit. Serious AEs recorded from the time of signing the informed consent up to and including the Week 12/ET Visit.

## 15.2 AE-QoL Score

How to calculate AE-QoL domain scores and AE-QoL total score

AE-QoL is meant to be evaluated by determining its four individual domain scores (application as a profile instrument) but it may also be used to determine a total score (application as an index instrument):

Each item answered by the patient scores between 0 and 4 points depending on the answer option chosen by the patient. The 1st answer option gets 0 points, the 2nd option 1point, the 3rd option 2 point, etc. The AE-QoL domain scores as well as the AE-QoL total score are calculated by using the following formula:

AE-QoL Score=(Sum of all completed items/Max. possible sum all completed items)*100

Example 1: All items were completed (Max. Possible Sum: 68 points
Sum of all 17 completed items : 41 points

(41/68) *100 =60 => AE -QoL Total score=60 out of possible 100 points

Example 2: 2 items were not completed (Max. possible sum: 60 points
Sum of all 15 completed items: 41 points.

(41/60) *100= 68 => AE -QoL Total Score = 68 out of possible 100 points

Computation of Domain Scores (Example: Fears/Shame):

Example: Sum of 6 completed items: 14 points
Max possible sum: 24 Points

(14/24)*100= 58 => Fears/Shame Score= 58 out possible 100 points

Remarks

Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0 to 100 scale), the calculated scores are not or only little influenced by missing items.

An AE -QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.

The minimal and highest possible domain and total scores are 0 and 100, respectively.

### 15.3 AECT Score

The AECT is a self-administered 4-item patient-reported outcome measure for patients with recurrent angioedema. Patients are asked to read the instructions of the AECT and to then provide answers to all 4 AECT-question. Subsequently, the AECT score can be computed. To this end, scores between 0 and 4 are assigned to the answer options of every AECT question and the scores of the chosen answer options are summed up. Accordingly, the minimum and maximum scores are 0 and 16., with higher scores indicating a higher level of angioedema control.

AECT Score= Score question 1+ score question 2 + score question 3 + score question 4

### 15.4 TSQM Score

TSQM scale scores computed by adding the items loading on each factor. The lowest possible score is subtracted from the composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that should be multiplied by 100. (see below). [Note that only one item may be missing from each scale before the subscale should be considered invalid for the respondent]

EFFECTIVENESS

{[(ITEM 1 + ITEM 2 +ITEM 3)-3] divided by 18} *100

If one item is missing
{[ (sum (ITEM 1 ? + ITEM 2? + ITEM 3 ?))-2] divided by 12} *100

SIDE -EFFECTS

If Question 4 is answered 'No' then score =100

Else
{[ sum (ITEM 5 to ITEM 8)-4] divided by 16}*100
If one item is missing
{[ sum (ITEM 5? to ITEM 8? )-3] divided by 12}*100

CONVENIENCE

{[ sum (ITEM 9 to ITEM 11)-3] divided by 18}*100
If one item is missing
{[ sum (ITEM 9? to ITEM 11? )-2] divided by 12}*100

GLOBAL SATISFACTION

{[ sum (ITEM 12 to ITEM 14)-3] divided by 14}*100
If either Item 12 or 13 is missing

{[ sum (ITEM 12? to ITEM 13?, ITEM 14)-2] divided by 10}*100

If item 14 is missing
{[ sum (ITEM 12 and ITEM 13 )-2] divided by 8}*100

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