Statistical Analysis Plan

KVD900-201

A randomized, double-blind, placebo-controlled, phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900, an oral plasma kallikrein inhibitor, in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema type I or II

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CONFIDENTIAL

Version	Author
Final 1.0	[redacted]

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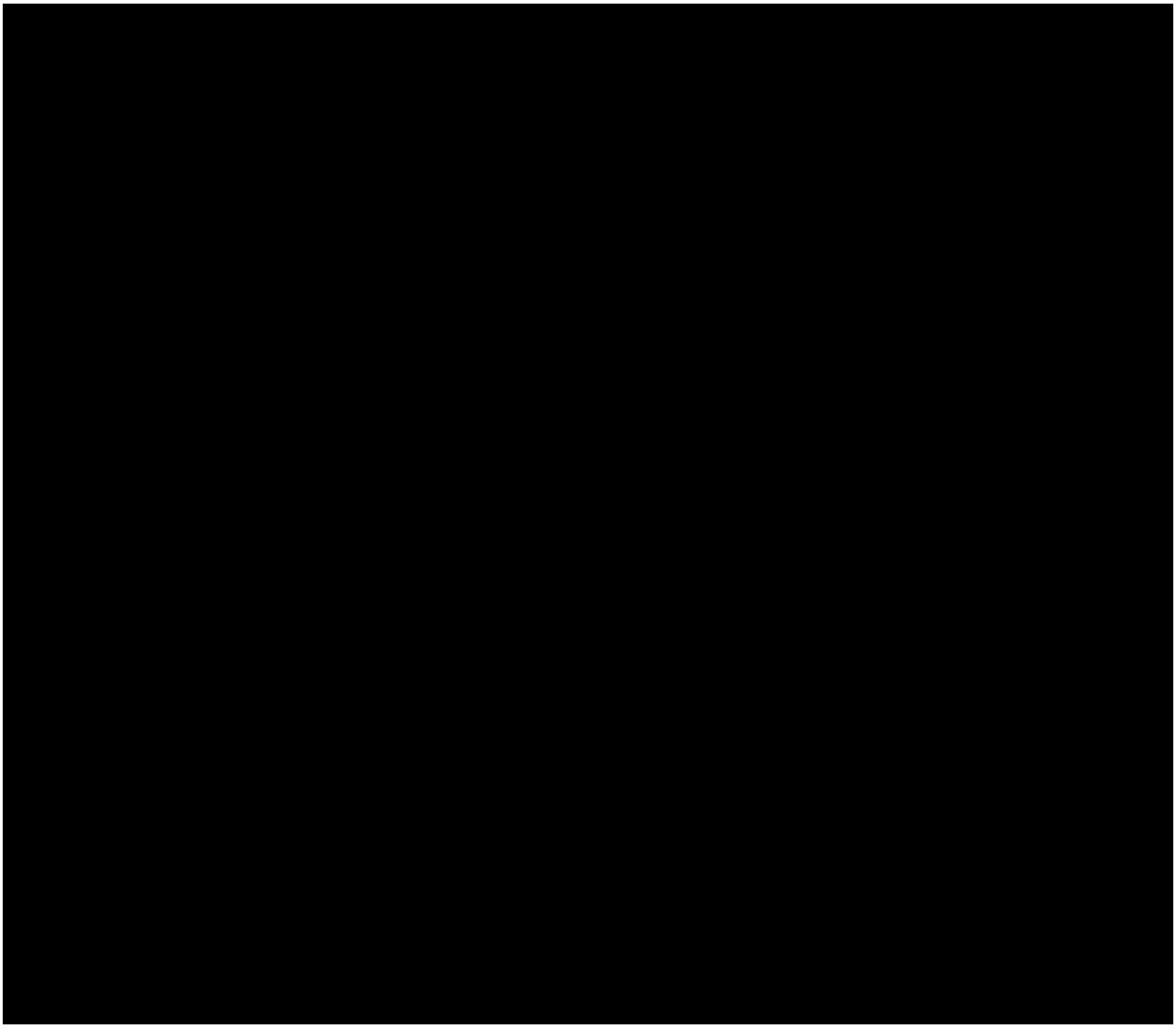
Author: [redacted]

Version: Final 1.0

The undersigned have reviewed and revised this SAP and find it to be consistent with the study requirements:

[redacted]



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GLOSSARY OF ABBREVIATIONS

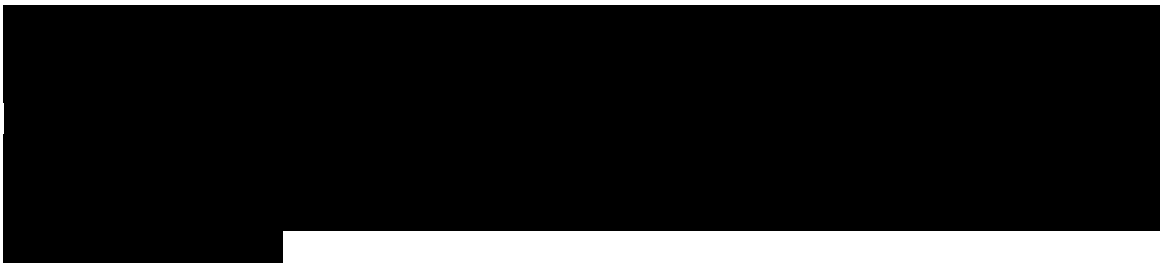
5LS	5-point Likert Scale
7TQ	7-point Transition Question
%CV	Coefficient of Variation
ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
$AUC_{\%extrapolated}$	Residual Area
$AUC_{0\text{-}inf}$	Area Under the Plasma Concentration-time Curve calculated from the time of dosing to infinity
$AUC_{0\text{-}t}$	Area Under the Plasma Concentration-time Curve calculated from the time of dosing to the last measurable concentration
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/F	Apparent clearance
C_{max}	Maximum observed plasma concentration
CRA	Clinical Research Associate
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DBL	Database Lock
DMP	Data Management Plan
DRM	Blind Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GM	Geometric Mean
HAE	Hereditary Angioedema
HK	High Molecular Weight Kininogen
HR	Heart Rate
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product

K_{el}	Elimination rate constant
LLOQ	Lower Limit of Quantitation
LOCF	Last Observation Carried Forward
LSMean	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre
n	Number of subjects with non-missing observations
N	Number of subjects in the Analysis Set
NCS	Not clinically significant
PD	Pharmacodynamic
PPS	Per Protocol Set
PK	Pharmacokinetic
PKa	Plasma Kallikrein
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
QC	Quality Control
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
$T_{1/2}$	Terminal elimination half-life
TEAE	Treatment Emergent Adverse Event
tmax	Time from dosing to the maximum observed plasma concentration
VAS	Visual Analogue Scale
Vd/F	Volume of distribution
WHO	World Health Organisation
WHODD	World Health Organisation Drug Dictionary

1 INTRODUCTION

1.1 GENERAL

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under KalVista Pharmaceuticals Protocol KVD900-201 and should be read in conjunction with the study protocol and electronic case report form (eCRF).



At the time of writing this version of the SAP, recruitment is complete.

Draft versions of the SAP will undergo review by the Statistical Reviewer, Statistical Programmer, Project Manager, PK Analyst, Medical Writer, Medical Monitor and the Sponsor/Sponsor representatives. The analysis plan will be finalised and approved by the Sponsor prior to Database Lock (DBL).

1.2 CHANGES FROM PROTOCOL

None.

1.3 CHANGES FROM PREVIOUS VERSIONS OF THE SAP

Not applicable.

2 STUDY OBJECTIVES

Primary Objective:

- To investigate the efficacy of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack of hereditary angioedema (HAE).

Secondary Objectives:

- To investigate the safety and tolerability of KVD900.
- To investigate the pharmacokinetic (PK) profile of KVD900 when taken during the intercritical period between HAE attacks.
- To investigate the pharmacodynamic (PD) profile of KVD900 in reducing the concentration of residual cleaved high molecular weight kininogen (HK) during the intercritical period between HAE attacks.
- To investigate the PD profile of KVD900 in reducing activated plasma enzyme activity during the intercritical period between HAE attacks.

3 STUDY DESIGN

3.1 OVERVIEW

This is a multicentre, phase I, randomized, two-part, two-sequence, two-period (2x2) cross-over clinical trial conducted in approximately 23 sites to evaluate the efficacy, safety and tolerability of KVD900 compared to placebo in halting the progression of a peripheral or abdominal attack in adult subjects with HAE type I or II. Approximately 60 male and female subjects will be enrolled into the study to ensure approximately 50 subjects complete.

The study will be conducted in two parts, with the same cohort of subjects participating in both parts.

Part 1
Subjects will receive a single oral dose of 600 mg KVD900 to investigate the safety, PK and PD of KVD900 during the intercritical period between HAE attacks. Eligible adult subjects ≥18 years old will undergo a screening assessment for study inclusion, receive study drug, followed by 4h, in-clinic, safety, PK and PD assessments.

PK and PD blood sampling will not take place for subjects who are enrolled under version 4.3, 5.0, 5.1 and 5.2 of the protocol. They will undergo safety assessments only.

Part 2
Subjects will be randomized 1:1 to two treatment sequences. This part of the study will occur away from the clinic or hospital.

In Sequence 1 (study arm 1) subjects will receive a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a single dose of placebo to treat the second eligible HAE attack.

In Sequence 2 (study arm 2) subjects will receive a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects will receive a single dose of 600 mg KVD900 to treat the second eligible HAE attack.

The final clinic visit will take place once both eligible HAE attacks have been treated. Since a sample size of 50 subjects is considered sufficient to address the primary efficacy hypothesis, once 50 subjects have completed both treatment periods further exposure is not required and could be considered unnecessary. Therefore, ongoing subjects who have not completed both periods will be asked to return to the study site and complete Visit 4 (Early Discontinuation visit).
The maximum duration of the study for each randomized subject is likely to be approximately 19 weeks.

3.2 INCLUSION AND EXCLUSION CRITERIA

To be eligible for inclusion into this study, each subject must fulfil all inclusion criteria and not violate any exclusion criteria (for the protocol version under which they are entered) during screening prior to randomization. Details of the inclusion and exclusion criteria are presented in protocol sections 4.1 and 4.2.

3.3 STUDY TREATMENT

Part 1

Under the supervision of the clinic staff, each subject will receive a single oral dose of the following:

- 6 x 100 mg KVD900 film coated tablets.

Part 2

Each subject will receive the following over 2 treatment periods (1/period) in accordance with the randomisation schedule:

- 6 x 100 mg KVD900 film coated tablets.
- Matching placebo.

When an attack of HAE occurs, the subject will telephone the dedicated study physician or qualified designee with a description of the HAE attack documented in the Subject Diary. This description will include:

- Attack location.
- Attack symptoms (e.g. swelling, pain, vomiting).
- Time of onset.
- Attack severity.
- Time of last substantial meal.

The dedicated study physician or qualified designee will assess the HAE attack against the following criteria for a qualifying attack:

- Attack location below the neck (laryngeal or facial attacks are not eligible).
- Attack onset < 1h.
- Attack severity less than severe on the Patient Global Impression of Severity (PGI-S) 5 point Likert scale (5LS).

The dedicated study physician or qualified designee will check that the appropriate washout periods for treatment with C1-INH or icatibant (all doses) have been respected prior to dosing with the study drug.

Having contacted the dedicated study physician or qualified designee with a description of the HAE attack symptoms and obtained the dedicated study physician or qualified designee's confirmation of HAE attack eligibility and agreement to use study drug, the subject will self-administer a single dose of KVD900 600 mg (6 x 100 mg tablets) or matching placebo tablets in response to the first qualifying attack of HAE. If the HAE attack is not eligible for treatment with the study drug, the subject will commence conventional attack treatment.

Subjects will return to the clinic following the first eligible HAE attack and will be dispensed the second study drug assigned in their respective administration sequence to take home for treatment of the second eligible HAE attack.

A minimum of 48 h washout period is required between each dose of study drug.

Conventional Attack Treatment

Conventional attack treatment is permitted after 4h, or earlier as warranted, following study drug intake, provided HAE attack symptoms are judged severe enough by the subject to require treatment as per the subject's usual treatment regimen, or are deemed ineligible for study drug treatment, or are associated with laryngeal or facial symptoms. Subjects are permitted to treat their HAE attacks with their conventional attack treatment (pdC1-INH or rhC1-INH iv or icatibant).

Subjects will attempt to contact their study physician or qualified designee prior to use of conventional attack treatment. The dedicated study physician or qualified designee should confirm that conventional attack treatment is appropriate per the protocol and HAE attack severity. Should the subject be unable to reach their study physician or qualified designee prior to taking conventional attack treatment, subjects may take their conventional attack treatment as needed.

In the event a subject receives treatment with C1-INH or icatibant (all doses) during the study, the following washout periods are required prior to the subsequent dosing with the study drug:

- 7-day washout period required for C1-INH.
- 3-day washout period required for icatibant.

3.4 Study Timepoints

Study visits will occur as follows:

	Visit	Time (relative to visit)
Screening	V1	V2 - 28 days
Part 1 Part 2: 1st eligible HAE attack	V2	
Washout (48 h minimum)* 2nd eligible HAE attack	V3	Within 7 days of 1st HAE attack
End of Study/Early Discontinuation	V4	Within 7 days of 2nd HAE attack

* In the event a subject receives treatment with C1-INH or icat bant (all doses) during the study, the washout periods required prior to the subsequent dosing with study drug are 7 days or 3 days respectively.

See Section 16.1 for the Study Schedule flowchart.

3.5 Sample Size Considerations

Approximately 60 subjects will be enrolled to ensure that approximately 50 subjects complete the study. A sample size of 50 subjects completing both treatment periods (25 per sequence) is proposed to provide 90% power for testing at the 5% alpha level (2-sided) for the primary endpoint of time to use of conventional attack treatment. [redacted]

[redacted]

An oversampling by 20% (10 subjects) is proposed to account for subjects that may not complete both treatment periods due to infrequent or ineligible HAE attacks or for subjects who discontinue the trial early, for whatever reason. Thus, study enrolment will be considered sufficient to address the primary efficacy hypothesis after 50 subjects have completed both treatment periods. Since further exposure is not required and could be considered unnecessary, ongoing subjects who have not completed both periods will be asked to return to the study site and complete Visit 4 (Early Discontinuation visit). Data from all subjects, complete and incomplete, will be analysed in the Safety Set.

3.6 RANDOMISATION

Permutated block randomization was used to create a randomization list to allocate subjects in the ratio 1:1 to the two sequences for Part 2 (KVD900 600 mg followed by placebo or placebo followed by KVD900 600 mg).

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

Subjects who satisfy all the entry criteria will be assigned to a treatment sequence according to the randomization scheme. Each randomized subject will receive a unique randomization number. Subjects will be randomized in a 1:1 ratio to Sequence 1 (KVD900 followed by placebo) or Sequence 2 (placebo followed by KVD900).

The actual treatment sequence for each subject will be determined by the randomization scheme. The final randomisation list will be generated and held by Simbec-Orion.
The randomization scheme will inform the Investigator of the kit ID number to be allocated to the subject in a blinded fashion.

The first dose of study drug will be the open label single 600 mg oral dose comprised of 6 x KVD900 100 mg Film Coated Tablets administered in the clinic during Part 1, after completion of all pre–dose assessments.

Randomized subjects who are discontinued from further study drug administration or are terminated from the study for any reason, regardless of whether study drug was taken or not, will not have their screening / randomization code be reused.

There is no randomization stratification in this study. Block sizes will be chosen by the Simbec-Orion statistician. The randomization will be programmed in SAS v9.3 by Simbec-Orion.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered onto the database and all data queries have been resolved, the assignment of subject to the analysis sets has been completed and the database has been locked.

4 STUDY VARIABLES AND COVARIATES

4.1 PRIMARY EFFICACY VARIABLE

The primary variable for statistical comparison between treatments in Part 2 of the study will be:

- Time to use of conventional attack treatment within 12h of study drug

4.2 Secondary Efficacy Variables

The following secondary efficacy variables will be analysed for Part 2 of the study:

- Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS):
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 12h of study drug
    - Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 12h of study drug
- Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ):
  - Improvement:
    - Time to symptom relief (*a little better* or higher for 2 consecutive time points) within 12h of study drug
- Visual Analogue Scale (VAS):
  - Improvement:
    - Time to symptom relief (50% reduction from baseline in composite VAS for 3 consecutive time points) within 12h of study drug

4.3 Exploratory Efficacy Variables

The following exploratory efficacy variables will be analysed for Part 2 of the study:

- Use of Conventional Treatment:
  - Proportion of HAE attacks that require conventional attack treatment within 12h and 24h of study drug
  - Time to use of conventional attack treatment within 24h of study drug

- PGI-S (5LS):
  - Area Under the Curve (AUC):
    - Cumulative PGI-S expressed as AUC within 12h and 24h of study drug
  - Worsening (including use of conventional attack treatment):
    - Proportion of HAE attacks that (1) worsen by one level or more from baseline or (2) use of conventional attack treatment within 24h of study drug
    - Time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 24h of study drug
  - Worsening Only:
    - Time to worsening by one level or more from baseline within 12h and 24h of study drug
  - Improvement:
    - Proportion of HAE attacks that improve by one level or more from baseline within 12h and 24h of study drug
    - Time to improvement by one level or more from baseline within 12h and 24h of study drug
    - Proportion of subjects with HAE attack resolution (rating of *none*) within 12h and 24h of study drug
    - Time to HAE attack resolution (rating of *none*) within 12h and 24h of study drug
  - Stable or Improvement:

        - Proportion of HAE attacks that are stable or improved from baseline within 12h and 24h of study drug

- PGI-C (7TQ):
    - AUC:
        - Cumulative PGI-C expressed as AUC within 12h and 24h of study drug
    - Worsening (including use of conventional attack treatment):
        - Proportion of HAE attacks that are (1) rated *a little worse* or higher for 2 consecutive time points, or (2) use of conventional attack treatment within 12h and 24h of study drug
        - Time to HAE attack being (1) rated *a little worse* or higher for 2 consecutive time points, or (2) use of conventional attack treatment, whichever comes first, within 12h and 24h of study drug
    - Worsening Only:
        - Time to HAE attack being rated *a little worse* or higher for 2 consecutive time points, within 12h and 24h of study drug
    - Improvement:
        - Proportion of HAE attacks that are rated *a little better* or higher for 2 consecutive time points, within 12h and 24h of study drug
        - Time to HAE attack being rated *a little better* or higher for 2 consecutive time points, within 24h of study drug
        - Proportion of HAE attacks that are rated *better* or higher within 12h and 24h of study drug
        - Time to HAE attack being rated better or higher within 12h and 24h of study drug
    - Stable or Improvement:
        - Proportion of HAE attacks that are stable or improved within 12h and 24h of study drug

- Visual Analogue Scale (VAS):
    - AUC:
        - Cumulative composite VAS expressed as AUC within 12h and 24h of study drug
    - Improvement:
        - Proportion of HAE attacks with symptom relief (50% reduction from baseline in composite VAS for 3 consecutive time points) within 12h and 24h of study drug
        - Time to symptom relief (50% reduction in composite VAS for 3 consecutive time points) within 24h of study drug

4.4 PHARMACOKINETIC VARIABLES

The derived plasma KVD900 variables for Part 1 of the study are as follows:

- C_{max} Maximum observed plasma concentration.
- t_{max} Time to maximum observed concentration.
- K_{el} Elimination rate constant.
- $t_{1/2}$ Terminal elimination half-life.
- AUC_{0-t} Area under the plasma concentration versus time curve (AUC) from the time of dosing to the time of last measurable concentration.

- $AUC_{0\text{-}inf}$ The AUC extrapolated to infinity.
- $AUC_{\%\ extrapolated}$ Residual area.
- CL/F Apparent clearance.
- Vd/F Volume of distribution.

4.5 PHARMACODYNAMIC VARIABLES

The following pharmacodynamic variables will be measured for Part 1 of the study to assess the effect of KVD900 on plasma kallikrein (PKa) enzyme activity:

[redacted]

4.6 SAFETY VARIABLES

Safety will be evaluated for Parts 1 and 2 by the following:

- Adverse events (AEs), including serious adverse events (SAEs).
- Laboratory test results (clinical chemistry, hematology, coagulation and urinalysis).
- Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature).
- Physical examination findings.
- 12-lead ECG results (HR, PR, RR, QRS, QT, QT corrected using Fridericia's formula (QTcF) and physician's review).

5 DEFINITIONS

Study Drug/Treatment: Study drug/treatment is taken to mean either KVD900 or placebo.

Baseline: Unless otherwise stated, baseline is defined by subject and by variable as the last non-missing value before each dose of study drug in Part 1 and Part 2. Details regarding endpoint-specific baselines are documented in Section 11, where appropriate.

Protocol Deviation: a deviation related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment. This refers to any change, divergence, or departure from the study design or procedures defined in the protocol. Deviations recorded by the Project Manager or Clinical Research Associate (CRA) or detected by Data Management or by statistical programming checks will be identified and discussed at the Blind Data Review Meeting (BDRM) before Database Lock (DBL).

6 ANALYSIS SETS

Membership of the analysis sets will be reviewed and agreed at a Data Review Meeting prior to Database Lock.

6.1 SAFETY SET

All subjects who receive at least one dose of study drug (including the study drug dose in Part 1) will constitute the Safety Set (SAF).

If one or more subject(s) received incorrect trial drug, data summarised using the SAF will be presented according to the treatment actually received.

Unless specified otherwise, the Safety Set will be used for all safety summaries as well as for all study listings. Demographic and baseline characteristics will be evaluated for the SAF, FAS and PPS.

6.2 FULL ANALYSIS SET

All randomized subjects who receive both doses of study drug in Part 2 will constitute the Full Analysis Set (FAS).

If one or more subject(s) received incorrect trial drug, data summarised using the FAS will be presented according to the planned treatment.

The FAS will be used for all efficacy analyses in Part 2 of the study. If more than 5 subjects do not complete both study periods, a supportive sensitivity analysis will be performed using the SAF (see section 11.3 for analysis details).

6.3 PER PROTOCOL SET

All randomized subjects who receive both doses of study drug in Part 2 and do not incur a major protocol deviation which may invalidate or bias the results will constitute the Per Protocol Set (PPS).

The primary efficacy analysis will be based on the FAS. A secondary efficacy analysis of the primary and secondary endpoints will also be performed using the PPS, should the FAS and PPS differ.

6.4 PK SET

Subjects who receive a dose of study drug in Part 1, have sufficient plasma KVD900 concentration-time profiles and comply with the following criteria will be included in the PK Set:

- Do not have an occurrence of vomiting or severe diarrhoea which renders the plasma concentration profile unreliable (e.g. if vomiting occurs at or before 2 times median t_{max});
- Do not use a concomitant medication which renders the concentration profile unreliable;
- Have at least one PK sample with a concentration above the lower limit of quantitation (LLOQ);
- Do not incur a major protocol deviation which may invalidate or bias the PK results.

Membership of the PK set will be reviewed and agreed at a BDRM prior to DBL, given the open-label nature of Part 1 of the study.

The PK Set will be used for PK data summaries.

7 SAFETY MONITORING

No interim safety analyses are planned for this study.

8 INTERIM ANALYSES

No interim efficacy analyses are planned for this study.

9 DATA

9.1 eCRF Data

eCRF data will be provided by Simbec-Orion Data Management to the Statistics department as SAS data sets in Simbec-Orion standard format. SDTM datasets will be derived from the raw database and ADaM from SDTM. Both SDTM and ADaM domains will be used for programming the outputs to be included in the Clinical Study Report (CSR). SDTM/ADaM programming will begin when populated Simbec-standard SAS datasets are available.

9.2 External Data

9.2.1 Safety Laboratory Data

With the exception of some local laboratory data which will be entered directly into the database, transfers of safety laboratory data will be provided by the central laboratory and delivered to Data Management via electronic transfer and stored within the study database. Details of laboratory data are documented in the Data Management Plan (DMP). Populated test transfers will be received to enable programming to commence. The following results will be included:

- **Hematology**: Erythrocytes, mean cell volume, mean cell haemoglobin, neutrophils(absolute and %), eosinophils (absolute and %), basophils (absolute and %), lymphocytes (absolute and %), monocytes (absolute and %), platelets, leukocytes, haemoglobin, haematocrit.
- **Clinical Chemistry including liver enzymes and electrolytes**: Glycosylated hemoglobin (HbA1c), creatinine, glucose, triglycerides, urea, uric acid, bilirubin, cholesterol, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, sodium, potassium, creatinine clearance.
- **Coagulation**: Prothrombin time, activated partial thromboplastin time.
- **Urinalysis:** pH, protein, glucose, ketones, bilirubin, blood, nitrite, albumin, microalbumin, , creatinine, albumin-creatinine ratio.
- **Pregnancy test:** Serum and urine pregnancy tests.

9.2.2 Other non-CRF data

9.2.2.1 Protocol Deviations

Protocol deviations will be recorded in an Excel spreadsheet by the Project Manager or CRA and stored as a SAS dataset. If applicable, any deviations detected by Data Management or by statistical programming checks will also be included in the SAS dataset. The protocol deviations will then be stored within the appropriate SDTM domain.

9.2.2.2 Pharmacokinetic Data

Plasma KVD900 concentration data will be delivered to Orion Data Management via electronic transfer from [redacted] and stored as a SAS dataset. Populated test transfers (using dummy data if necessary) will be received to enable programming to commence. The plasma concentration data will then be stored in the appropriate SDTM domain, which will be used to produce the file provided to the Simbec pharmacokinetic team in order to derive the PK parameters using Phoenix WinNonlin v8.1 or higher, and subsequently stored in the ADaM domain. Derived PK parameters will be received by the Statistics department from the PK Analyst in a SAS .xpt file in an agreed format and then stored as a SAS dataset within SDTM/ADaM domains.

9.2.2.3 Pharmacodynamic Data

[redacted]

9.3 Randomization List

The randomization list will be uploaded as a SAS dataset and incorporated into the relevant SDTM/ADaM domains following Database Lock.

9.4 Programming and Data Review

Programming of datasets, tables, figures and listings will be ongoing while study data management activities are in progress.

Prior to DBL, a dry-run delivery of a predetermined set of blinded Tables, Figures and Listings (TFLs) will be provided for Sponsor review.

Additionally, once the database is considered clean and has been frozen prior to DBL, a blind data review of the clinical database will be conducted. Outputs for the data review will be provided to the study team as Excel outputs of the clinical database. A BDRM will be held to discuss the outcome of this review, the imputations for the study endpoints, any potential impact on the analyses, analysis sets and protocol deviations. Meeting minutes will be created and, once all data issues have been resolved, the analysis sets approved and protocol deviation classifications agreed, the database will be locked. These minutes will be finalised and signed off prior to DBL. Once the aforementioned actions have taken place the database can be locked. The post-lock SDTM/ADaM datasets will be generated, the TFLs will be run and quality control (QC) will take place. Topline TFLs will be identified with *** in Section 14 List of Tables, Figures and Listings.

10 STATISTICAL METHODS

10.1 General Principles

- All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".
- Unless stated otherwise, safety data will be summarised by study part, treatment and overall (treatments combined) and efficacy data by treatment. Baseline data will be summarised by sequence group and overall (both sequence groups combined). Where appropriate, data will also be summarised by visit. The format of the summaries is defined in the shells in section 15.
- Repeated visits will be denoted with an 'Rpt'. Unscheduled visits will be denoted with an 'Uns'.
- For post-dose assessments, only data obtained from scheduled visits/time points will be used in summary tables. Post-dose repeat or unscheduled assessments will be listed only. For assessments occurring prior to dosing (e.g. Screening, Visit 2 pre-dose), the last repeat assessment for each visit will be included in the summary tables and, where repeats of baseline values occur, the last assessment will be used to calculate change from baseline.
- Where Visit 3 or Visit 4 took place outside of the 7 days post-dose visit window, results will be included within the summary tables but will be flagged within the listings.
- If more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. Invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient or other conditions that would render values invalid).
- In summary and analysis tables of continuous variables, standard descriptive statistics (number of subjects in the analysis set (N), number of subjects with non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum) will be presented. For PK summaries, geometric mean (GM) and CV% will also be used to summarise the data. For efficacy data summaries, Q1 (25th percentile), Q3 (75th percentile), least squares mean (LSMean) and 95% confidence interval (CI) will also be presented.
- Unless otherwise specified, the minimum and maximum statistics will be presented in summary tables to the same number of decimal places as the original data. The mean, LSMean, median, Q1, Q3 and CIs will be presented to one more decimal place than the original data. SD will be presented to two more decimal places than the original data.
- Derived PK and plasma concentration data will be presented to 3 significant figures within listings and summaries.
- With the exception of PK data, numeric data which includes non-numeric values (e.g. laboratory results reported as $<x$, $\leq x$, $\geq$x or $>x$), will be displayed within the data listings as recorded. For the derivation of listing flags, calculation of summary statistics and presentation in figures, results of $<x$ or $\leq x$ will be set to ½x and results of $\geq$x or $>x$ will be set to x.
- In summary tables of categorical variables, the number of non-missing observations by category will be presented with percentages. The number of missing observations will also be presented when non-zero. Unless otherwise specified, the denominator for each percentage will be the number of observations within the treatment/visit. All percentages will be presented to one decimal place.
- With the exception of PK data, plots will use a linear time scale for the nominal times of the visits and will be labelled by time point.
- Dates and times for all output presentations will be presented in ISO 8601 Datetime format.
- All outputs will present data in a format that complies with CDISC required terminology and codelists and the SAP will use American-English spelling in line with CDISC terminology, where appropriate (i.e. hematology).
- All statistical analysis will be performed using SAS 9.4.

- Generally, character values will be left aligned and numeric values will be decimally aligned.
- If no data is available for a specific output, the output will be produced stating an appropriate message indicating no data was present.
- Unless stated otherwise, classifications of medical history, concomitant medication and adverse events will be sorted alphabetically within the summary tables.
- All data collected on the eCRF will be presented within data listings. The data listings will generally be sorted by study part, subject number and visit/time point. If any subjects receive the wrong treatment this will be flagged in all listings. Visits outside the visit windows will be identified within the listings.
- All hypothesis testing will be carried out at the 5% (2-sided) significance level unless stated otherwise.
- P-values will be rounded to four decimal places. P-values less than 0.0001 will be reported as <0.0001 in tables.
- If any of the assumptions underlying the formal statistical methods proposed are violated during the analysis of the final data, alternative statistical methods will be used and any changes documented in the clinical study report (CSR), including the rationale for use.

10.2 Stratification and Covariate Adjustment

Randomization was not stratified.

10.3 Interactions

There will be no analysis of interactions.

10.4 Missing Data

Safety Data
No methods to impute missing safety data will be used.

Pharmacokinetic Data
In the instance of missing pharmacokinetic blood samples, the trapezoidal rule will be employed between the samples immediately before and after the missing sample for the AUC calculations.

Efficacy Data
For inclusion within the efficacy analyses, results obtained after use of conventional attack treatment will be considered as missing.

No methods to impute missing data will be used for the time to event analyses, summaries of categorical data or for the comparisons of proportions. However, descriptive statistics and plots over time of the numerical recoding of the PGI-S and PGI-C results, the VAS scores and the composite and Index VAS scores will be performed with and without the Last Observation Carried Forward (LOCF) method of imputation, such that any missing values prior to use of conventional attack treatment will be imputed, as will values obtained post-use of conventional attack treatment. Further details can be found in section 11.3.2.

10.5 Pooling of Sites

Sites will be pooled for all analyses. There will be no adjustment for centre effect or treatment by centre interaction.

10.6 Multiple Comparisons

No multiplicity adjustments are planned.

10.7 Subgroup Analyses

The primary endpoint, time from study drug administration to use of conventional attack treatment within 12 hours, will also be summarised descriptively by primary attack location (see section 11.3.1 for details).

10.8 Statistical Issues

The efficacy analysis is planned to be performed using the FAS (and PPS should they differ) which, by definition, requires subjects to have completed both treatment periods. This is necessary to facilitate the analysis of the efficacy data using [redacted]. However, failure to complete both treatment periods may be influenced by treatment or disease severity and the exclusion of these subjects may bias results. Therefore, if more than 5 subjects fail to complete both treatment periods, a sensitivity analysis of the primary and secondary efficacy endpoints will be performed using the SAF, consisting of Kaplan-Meier/survival estimates and descriptive statistics/frequencies as appropriate.

11 STATISTICAL OUTPUT

General principles for layout of the statistical output are described in Section 10.1. Layout and specifications are illustrated for each unique table and listing within the shells presented in Section 15.

11.1 Subject Disposition

A summary of the number of enrolled (screened) subjects, randomized subjects, screening/baseline failures (baseline failures identified by an answer of 'No' to the question *Is the subject still eligible?* on the Study Drug Dosing form) and reasons for screening/baseline failure will be produced for all enrolled subjects (*Table 14.1.1.1*). Subjects who were re-screened under a different screening number to that which was originally assigned will contribute only one count towards the number of enrolled subjects.

The number (%) of subjects dosed in Part 1, dosed with each treatment in Part 2, completed or withdrew from the study and the main reason for withdrawal will be summarised for all randomized subjects (*Table 14.1.1.2*).

The number (%) of subjects included within each analysis set will also be summarised (*Table 14.1.1.3*).

Study completion/withdrawal data will also be listed (*Listing 16.2.1.2, 16.2.1.3, 16.2.1.4*). A listing of all protocol deviations will be presented including major/minor classification (*Listing 16.2.2.1*). A data listing

presenting subject eligibility for each analysis set and the reason for exclusion from an analysis set will also be presented (*Listing 16.2.3.1*).

11.2 Subject Characteristics at Baseline

11.2.1 Demographics and Baseline Characteristics

Demographic data (including date/time of randomization) will be listed (*Listing 16.2.4.1*) and descriptive statistics for the continuous variables age, height, weight and BMI and frequencies for the categorical variables gender, race and ethnicity will be tabulated by treatment sequence and overall (*Table 14.1.2.1*).

Demographic and baseline data will be listed using the SAF and summarised for the SAF, FAS and PPS (if different from SAF).

11.2.2 Medical History and Current Medical Conditions

All conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0a. Past medical/surgical history (conditions which stopped prior to or at the Screening visit) and current medical conditions (conditions which are ongoing at and continue after Screening) will be listed (*Listing 16.2.4.2*) and summarised by system organ class (SOC) and preferred term (PT). The number (%) of subjects reporting each condition will be presented by treatment sequence and overall (*Table 14.1.2.2, 14.1.2.3*).

Medical history and current medical conditions will be listed and summarised using the SAF.

11.2.3 Disease History

HAE disease history data will be listed (*Listing 16.2.4.3*) and descriptive statistics for the continuous variables time since first HAE diagnosis, most recent C1-INH antigenic level, most recent C1-INH functional level, most recent C4 level and frequencies for the categorical variable family history of HAE (Yes/No) will be tabulated by treatment sequence and overall (*Table 14.1.2.4*).

Additionally, HAE attack profile in the 93 days prior to Screening, including the number of attacks, location of the attacks and maximum severity of attacks, will also be listed (*Listing 16.2.4.4*).

HAE disease history will be listed and summarised using the SAF.

11.3 Efficacy Analyses (Part 2 only)

Treatment comparisons will be KVD900 versus placebo. Efficacy data will be listed using the SAF and summarised primarily using the FAS. A secondary efficacy analysis of the primary and secondary endpoints will also be performed using the PPS, should the FAS and PPS differ. In addition, if more than 5 subjects do not complete both study periods, a sensitivity analysis of the primary and secondary endpoints will be performed using the SAF.

Unless stated otherwise, only results obtained prior to conventional attack treatment use will be included within the following efficacy analyses.

11.3.1 Primary Efficacy Analysis

In Part 2 of the study, following an HAE attack, subjects will be required to record in their diary the date and time that conventional attack treatment was taken, if taken. The primary efficacy endpoint, time from study drug administration to use of conventional attack treatment within 12 hours, will be expressed in hours and derived as follows:

Time to use of conventional attack treatment within 12 hours (h) = Date/time of conventional attack treatment use – Date/time of study drug administration

Subjects will be treated as right-censored if no conventional attack treatment is taken within 12h of study drug administration (plasma KVD900 levels are expected to be low by 12h). Any right-censored results will be flagged with 'R'.

The null hypothesis is that there is no difference between the time to use of conventional attack treatment following KVD900 treatment and the time to use of conventional attack treatment following placebo:

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

where t_k is the time to use of conventional attack treatment following KVD900 and t_p is the time to use of conventional attack treatment following placebo.

The alternative hypothesis is that the time to use of conventional attack treatment following KVD900 treatment is different from the time to use of conventional attack treatment following placebo:

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

Time to use of conventional attack treatment will be analysed using [redacted] which is appropriate for the crossover design of this study. [redacted]

The following steps should be performed to implement this test:

[redacted]

HAE attack information will be listed (*Listing 16.2.6.1, 16.2.6.2*). The time to conventional attack treatment use will be listed with censored observations flagged (*Listing 16.2.6.3*). Frequencies (n, %) of subjects that used conventional attack treatment or were censored will be presented. Kaplan-Meier estimates of the 25th percentile (Q1), the median and corresponding 95% CI of time to conventional attack treatment use will be presented by treatment (KVD900 / placebo), along with [redacted] p-value (*Table 14.2.1.1*). Kaplan-Meier survival curves will also be presented by treatment (*Figure 14.2.1.1*). Kaplan-Meier survival analysis will be performed using the SAS LIFETEST procedure as is appropriate for right censored data.

In addition, a subgroup analysis of the primary efficacy endpoint will be performed by primary attack location at HAE attack onset. Frequencies (n, %) of subjects that used conventional attack treatment or were censored will be presented by primary attack location, along with Kaplan-Meier estimates (*Table 14.2.1.2*) and survival curves (*Figure 14.2.1.2*).

If more than 5 subjects do not complete both study periods, a sensitivity analysis will be conducted using the SAF. Frequencies (n, %) of subjects that used conventional attack treatment or were censored will be presented along with Kaplan-Meier estimates and survival curves.

11.3.2 Secondary Efficacy Analysis

In Part 2, following study drug intake, subject assessments of overall HAE attack severity and change in HAE attack severity will be undertaken as follows:

Table 1: Frequency of Subject Assessment of HAE Attack Severity

Time Interval Post-Study Drug Administration	**Frequency of Subject Assessment***	**Permissible Window**
0h – 4h	Every 30 min	None
4h – 12h	Every 1h	± 15 min
12h – 24h	Every 3h	± 30 min
36h	Once	± 60 min
48h	Once	± 60 min

* In the event that conventional attack treatment is used, the subject should perform assessments every 30 min for 4h following first administration of conventional attack treatment. After this, the subject should revert to original frequency of assessments based on time of study drug administration.

HAE attack severity will be assessed on the Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS) scored as *none, mild, moderate, severe* and *very severe*.

Change in HAE attack severity will be assessed using the Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ) scored as *much better, better, a little better, no change, a little worse, worse, much worse.*

The type of HAE attack symptoms (abdominal pain, skin pain, skin swelling) will each be assessed on a 100 mm visual analogue scale (VAS) ranging from 0 (none) to 100 (very severe). The composite VAS score will be derived as the average score across the three symptoms. The Index VAS score is defined as the symptom with the highest score at baseline or, in the instance of two or more symptoms having an identical baseline score, the average of these scores.

HAE attack severity, change in HAE attack severity and HAE attack symptoms VAS scores will be listed (*Listing 16.2.6.1, 16.2.6.2, 16.2.6.3*).

Frequencies (n, %) of the HAE attack severity and change in attack severity will be presented by time point and treatment (*Table 14.2.2.1, 14.2.2.2*). Frequencies (n, %) of the time point of worsening in HAE attack severity on the PGI-S by one level or more will also be presented (*Table 14.2.2.3*).

The PGI-S scores will be transformed into numeric values (recoded as 0 (none) to 4 (very severe)) and descriptive statistics (N, n, mean, SD, minimum, Q1, median, Q3 and maximum, and 95% CI) of absolute and change from baseline values will be presented by time point and treatment (*Table 14.2.2.4*). The mean absolute and change from baseline values will also be presented graphically over time *(Figure 14.2.2.1, 14.2.2.2)*.

The PGI-C scores will be transformed into numeric values (recoded as -3 (much better) to 3 (much worse)) and descriptive statistics (N, n, mean, SD, minimum, Q1, median, Q3 and maximum, and 95% CI) will be presented by time point and treatment (*Table 14.2.2.6*). The mean values will also be presented graphically over time time *(Figure 14.2.2.5)*.

The descriptive statistics and plots over time of the recoded numeric values of the PGI-S and PGI-C results as described above will be performed with and without the LOCF method of imputation, such that any missing values prior to use of conventional attack treatment will be imputed, as will values obtained post-use of conventional attack treatment (*Table 14.2.2.5, 14.2.27, Figure 14.2.2.3, 14.2.2.6*).

Descriptive statistics (N, n, mean, SD, minimum, Q1, median, Q3, maximum and 95 % CI) of absolute and change from baseline (pre-dose) HAE attack symptoms VAS scores will be tabulated by time point and treatment (*Table 14.2.2.8*The descriptive statistics and plots over time of the VAS scores and the composite and Index VAS scores as described above will be performed with and without the LOCF method of imputation, such that any missing values prior to use of conventional attack treatment will be imputed, as will values obtained post-use of conventional attack treatment (*Table14.2.2.9, 14.2.2.11, 14.2.2.13, Figure 14.2.2.9, 14.2.2.10, 14.2.2.13, 14.2.2.14, 14.2.2.17, 14.2.2.18*).

If more than 5 subjects do not complete both study periods, the above summaries will also be presented for the SAF.

11.3.2.1 Secondary Efficacy Variable 1

- Time from study drug administration to either (1) worsening in attack severity by one level or more from baseline on the PGI-S, or (2) use of conventional attack treatment (as defined in section 11.3.1), whichever comes first within 12 h.

Time to worsening in attack severity by ≥ 1 level (h) = Date/time of first increase in severity – Date/time of study drug administration

Time to use of conventional attack treatment (h) = Date/time of conventional attack treatment use – Date/time of study drug administration

[redacted]

If more than 5 subjects do not complete both study periods, a sensitivity analysis will be conducted using the SAF. Frequencies (n, %) of subjects experiencing a worsening on the PGI-S by one level or more or using conventional attack treatment and the number censored will be presented, along with survival estimates and survival curves.

11.3.2.2 Secondary Efficacy Variable 2

- Proportion of HAE attacks that worsen by one level or more from baseline on the PGI-S or that require conventional attack treatment within 12h of study drug.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.3.2.3 Secondary Efficacy Variable 3

- Time to symptom relief, defined as the HAE attack being rated *a little better* or higher on the PGI-C for two consecutive time points, within 12h of study drug.

Time to HAE attack being rated *a little better* or higher for 2 consecutive time points (h) = Date/time of first rating of *a little better* or higher which is immediately followed by another rating of *a little better* or higher (with no missing values in between) – Date/time of study drug administration

[redacted]

If more than 5 subjects do not complete both study periods, a sensitivity analysis will be conducted using the SAF. Frequencies (n, %) of subjects rating the HAE attack as *a little better* or higher for two consecutive time points and the number censored will be presented, along with survival estimates (*Table 14.2.2.16*) and survival curves (*Figure 14.2.2.20*).

11.3.2.4 Secondary Efficacy Variable 4

- Time to symptom relief, defined as a 50% reduction in composite VAS score for three consecutive time points, within 12h of study drug.

Time to 50% reduction in composite VAS score for 3 consecutive time points (h) = Date/time of first reduction in composite VAS score of ≥ 50% from baseline which is immediately followed by two consecutive composite score reductions of ≥ 50% (with no missing values in between) – Date/time of study drug administration

[redacted]

If more than 5 subjects do not complete both study periods, a sensitivity analysis will be conducted using the SAF. Frequencies (n, %) of subjects with a 50% reduction in composite VAS score for 3 consecutive time points and the number censored will be presented, along with survival estimates and survival curves.

11.3.3 Exploratory Efficacy Analysis

11.3.3.1 Exploratory Efficacy Variable 1

- Proportion of HAE attacks that require conventional attack treatment within 12h and 24h of study drug.

[redacted]

11.3.3.2 Exploratory Efficacy Variable 2

- Time to use of conventional attack treatment within 24h of study drug.

Time to use of conventional attack treatment within 24 hours (h) = Date/time of conventional attack treatment use – Date/time of study drug administration

[redacted]

11.3.3.3 Exploratory Efficacy Variable 3

- Cumulative global attack severity on the PGI-S expressed as area under the curve (AUC) within 12h and 24h of study drug.

[redacted]

11.3.3.4 Exploratory Efficacy Variable 4

- Proportion of HAE attacks that worsen in severity by one level or more from baseline on the PGI-S or that require conventional attack treatment within 24h of study drug.

[redacted]

11.3.3.5 Exploratory Efficacy Variable 5

- Time from study drug administration to either (1) worsening in attack severity by one level or more from baseline on the PGI-S, or (2) use of conventional attack treatment, whichever comes first within 24h [as defined in section 11.3.2.1].

[redacted]

11.3.3.6 Exploratory Efficacy Variable 6

- Time from study drug administration to worsening in attack severity by one level or more from baseline on the PGI-S within 12h and 24h,

[redacted]

[redacted]

11.3.3.7 Exploratory Efficacy Variable 7

- Proportion of HAE attacks that improve by one level or more from baseline on the PGI-S within 12h and 24h of study drug.

[redacted]

11.3.3.8 Exploratory Efficacy Variable 8

- Time to improvement in HAE attack severity from baseline by one level or more on the PGI-S within 12h and 24h of study drug.

[redacted]

11.3.3.9 Exploratory Efficacy Variable 9

- Proportion of subjects with HAE attack resolution, defined as a rating of *None* on the PGI-S, within 12h and 24h of study drug.

[redacted]

11.3.3.10 Exploratory Efficacy Variable 10

- Time from study drug administration to complete HAE attack resolution within 12h and 24h, defined as a rating of *None* on the PGI-S.

Time to HAE attack resolution (h) = Date/time of first rating of *None* – Date/time of study drug administration

[redacted]

11.3.3.11 Exploratory Efficacy Variable 11

- Proportion of HAE attacks that are stable or improved in severity (defined as not worsening by one level or more from baseline) on the PGI-S within 12h and 24h of study drug.

[redacted]

11.3.3.12 Exploratory Efficacy Variable 12

- Cumulative change in HAE attack severity on the PGI-C expressed as AUC within 12h and 24h of study drug.

[redacted]

11.3.3.13 Exploratory Efficacy Variable 13

- Proportion of HAE attacks that are (1) rated *a little worse* or higher on the PGI-C for two consecutive time points or (2) use of conventional attack treatment, within 12h and 24h of study drug.

[redacted]

11.3.3.14 Exploratory Efficacy Variable 14

- Time to HAE attack being (1) rated *a little worse* or higher on the PGI-C for two consecutive time points or (2) use of conventional attack treatment, whichever comes first, within 12h and 24h of study drug.

[redacted]

[redacted]

11.3.3.15 Exploratory Efficacy Variable 15

- Time to HAE attack being (1) rated *a little worse* or higher on the PGI-C for two consecutive time points within 12h and 24h of study drug.

[redacted]

11.3.3.16 Exploratory Efficacy Variable 16

- Proportion of HAE attacks that are rated *a little better* or higher on the PGI-C for two consecutive time points within 12h and 24h of study drug.

[redacted]

11.3.3.17 Exploratory Efficacy Variable 17

- Time to symptom relief, defined as the HAE attack being rated *a little better* or higher on the PGI-C for two consecutive time points, within 24h of study drug.

Time to HAE attack being rated *a little better* or higher for 2 consecutive time points (h) = Date/time of first rating of *a little better* or higher which is immediately followed by another rating of *a little better* or higher (with no missing values in between) – Date/time of study drug administration

[redacted]

11.3.3.18 Exploratory Efficacy Variable 18

- Proportion of HAE attacks that are rated *better* or higher on the PGI-C within 12h and 24h of study drug.

[redacted]

11.3.3.19 Exploratory Efficacy Variable 19

- Time to HAE attack being rated *better* or higher on the PGI-C within 12h and 24h of study drug.

[redacted]

11.3.3.20 Exploratory Efficacy Variable 20

- Proportion of HAE attacks that are stable or improved (defined as not rating a little worse, worse or much worse, 2 time points in a row) on the PGI-C within 12h and 24h of study drug.

[redacted]

11.3.3.21 Exploratory Efficacy Variable 21

- Cumulative composite VAS score expressed as AUC within 12h and 24h of study drug.

[redacted]

[redacted]

11.3.3.22 Exploratory Efficacy Variable 22

- Proportion of HAE attacks with symptom relief, defined as a 50% reduction in composite VAS for three consecutive time points, within 12h and 24h of study drug.

[redacted]

11.3.3.23 Exploratory Efficacy Variable 23

- Time to symptom relief, defined as a 50% reduction in composite VAS for three consecutive time points, within 24h of study drug.

Time to symptom relief is calculated as the earliest occurring of the following:

Time to 50% reduction in composite VAS score for 3 consecutive time points (h) = Date/time of first reduction in composite VAS score of ≥ 50% from baseline which is immediately followed by two consecutive composite score reductions of ≥ 50% (with no missing values in between) – Date/time of study drug administration.

[redacted]

11.4 PK Analyses – Part 1

11.4.1 Plasma Concentration Data

For those who have samples taken for PK analysis, plasma PK samples will be collected for measurement of KVD900 during Part 1 of the study (Visit 2) at pre-dose (0 h), 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h and 4 h post-dose.

For inclusion within the summary tables and plots, BLQ concentrations will be imputed as zero at pre-dose and as 1/2 of LLOQ for post-dose samples. They will be listed as recorded.

For inclusion within the summary tables and figures, when calculating the geometric mean concentrations at pre-dose where zero values are likely to be observed, a small value (0.001) (or smaller if required by the data) will be added to all individual subject pre-dose concentration values prior to calculation of the mean. This value will then be subtracted after back-transformation, i.e.

$$Geometric\ Mean = exp(\frac{1}{n}\sum_{i=1}^{n}\log(x_i + 0.001)) - 0.001$$

where x_i are the individual concentration values at pre-dose.

This method is only required for pre-dose results as zero values will not occur for post-dose time points. For post-dose time points, the geometric mean will be calculated using the standard formula:

$$Geometric\ Mean = exp(\frac{1}{n}\sum_{i=1}^{n}\log(x_i)).$$

KVD900 concentrations in plasma will be listed (*Listing 16.2.5.11*) with any sample time deviations outside the permissible time window flagged, and summarised using the descriptive statistics N, n, arithmetic mean, geometric mean, arithmetic standard deviation (SD), coefficient of variation (%CV), minimum, median and maximum (*Table 14.4.1.1*).

The individual subject plasma KVD900 concentration profiles over time will be presented graphically on a linear and semi-logarithmic scale, with one plot per subject (*Figure 16.2.25.1, 16.2.5.2*). The x-axis will display the planned sampling times but the concentrations will be presented at the actual time the sample was taken. The geometric mean plasma concentration profile over time will be presented on linear and semi-logarithmic scales using the planned sampling times (*Figure 14.4.1.1, 14.4.1.2*).

The plasma concentration data listing and individual plots will be presented using the Safety Set. The plasma concentration data summary and mean plots will be presented using the PK Set. All plasma concentration data included in the listing and summary will be presented to three significant figures.

11.4.2 PK Parameters

The derived pharmacokinetic parameters of KVD900 in plasma will be determined using Phoenix WinNonlin v8.1 (or higher) from the individual concentration versus time data. For the purpose of calculating PK parameters, BLQ values will be imputed as zero at pre-dose and set to missing for post-dose time points. The actual time of blood sample will be used in the calculation of the derived pharmacokinetic parameters. The blood sampling time deviation will be calculated as actual date/time – theoretical date/time, where theoretical date/time is derived from the date/time of dose administration and nominal sampling time. Should the actual time be unavailable but a blood sample was taken, the nominal time point will be assigned.

The following PK parameters will be calculated using standard non-compartmental methods:

Pharmacokinetic Parameter	Definition	WinNonlin computation	WinNonlin Parameter Name
C_{max}	Maximum observed plasma concentration.	Maximum observed concentration, occurring at T_{max}. If not unique, then the first maximum is used.	Cmax
t_{max}	The time of maximum observed concentration.	Time of maximum observed concentration. If the maximum observed concentration is not unique, then the first maximum is used.	Tmax
AUC_{0-t}	Area under the plasma concentration-time curve (AUC) from the time of dosing to the time of the last measurable concentration.	AUC measured from the concentration at time of dosing to the last measurable positive concentration. The AUCs are computed using the Linear Up-Log Down method.	AUClast
K_{el}	Elimination rate constant.	First order rate constant associated with the terminal (log-linear) portion of the curve. Estimated by linear regression of time vs. log concentration; the regression analysis should contain data from at least 3 different time points in the terminal phase, not including Cmax, and an R^2-adjusted of at least 0.8.	Lambda_z
$t_{1/2}$	Terminal elimination half-life.	$= \ln(2) / K_{el}$	HL_Lambda_z
AUC_{0-inf}	AUC extrapolated to infinity.	AUC measured from the concentration at time of dosing extrapolated to infinity based on the last observed concentration. $= AUC_{0-t} + \frac{C_{lastobs}}{K_{el}}$	AUCINF_obs
$AUC_{\% extrap}$	Residual area.	Percentage of AUC_{0-inf} due to extrapolation from time of last measurable positive concentration to infinity. $= \frac{AUC_{0-inf} - AUC_{0-t}}{AUC_{0-inf}} \cdot 100$	AUC_%Extrap_obs

CL/F	Apparent total body clearance following an extravascular dose.	$= Dose/AUC_{0-inf}$	Cl_F_obs
Vd/F	Apparent volume of distribution based on the terminal phase following an extravascular dose.	$= \frac{Dose}{K_{el}.AUC_{0-inf}}$	Vd_F_obs
K_{el} lower (listed only)	Elimination rate constant lower limit.	Lower limit on time for values to be included in the calculation of k_{el}	Lambda_z_lower
K_{el} upper (listed only)	Elimination rate constant upper limit.	Upper limit on time for values to be included in the calculation of k_{el}	Lambda_z_upper
No. points K_{el} (listed only)	Number of points used for elimination rate constant.	Number of points used for elimination rate constant	No_points_ Lambda_z
R^2 adjusted (listed only)	R^2 adjusted.	Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el}	Rsq_adjusted

Derived pharmacokinetic parameters will be listed (*Listing 16.2.5.2*) and summarised using the descriptive statistics N, n, arithmetic mean, arithmetic standard deviation (SD), coefficient of variation (%CV), minimum, median, maximum and geometric mean [with the exception of T_{max}] (*Table 14.4.2.1*).

The PK parameter data listing will be presented using the Safety Set. The PK data summary will be presented using the PK Set.

11.5 PD ANALYSES – PART 1

All PD parameters will be handled in a stand-alone PD analysis plan and will be reported in a self-contained PD analysis report.

11.6 SAFETY ANALYSES

11.6.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.0.

An AE will be classified as treatment-emergent if it started on or after the first date and time of study drug dosing at Visit 2 (Part 1) up to study closure or withdrawal date or if it was present prior to receipt of study drug but worsened in severity or increased in frequency after the first dose of study drug. Where there are only partial dates/times recorded for an AE, the start day, month, year or stop date

will be used to determine whether the AE is treatment-emergent. An AE will be assigned to the most recent treatment if it starts on or after the corresponding dose. Where there are only partial dates/times recorded for an adverse event, the adverse event will be assigned to every treatment (as an On-treatment TEAE) where it cannot be ruled out based on the partial information and flagged within the data listing. TEAEs will be summarised by study part and treatment, both active treatment periods combined and overall (all treatment periods combined).

Treatment-emergent adverse events (TEAEs) will be further classified as follows:

[redacted]

Post-treatment TEAEs: AEs occurring >48h post dose and prior to next dose administration, where appropriate.

Severe TEAEs: Severity classified as 'Severe' or missing.

Serious TEAEs: Serious classified as 'Yes' or missing.

Drug-related TEAEs: Relationship to study drug classified as 'Suspected' or missing.

Serious drug-related TEAEs: Both serious and drug-related, as specified above.

TEAEs leading to withdrawal from study: Action taken classified as 'Drug withdrawn'.

TEAEs leading to death: Outcome classified as 'Fatal'.

An overall summary of TEAEs will be produced presenting the number of TEAEs reported and the number and percentage of subjects reporting TEAEs within the categories listed above. A subject with multiple occurrences of AEs will be counted only once within a category (*Table 14.3.1.1*). This table will be repeated for [redacted] (as defined above) (*Table 14.3.1.2*).

Unless specified otherwise, the following summary tables will be produced including all TEAEs (regardless of relationship to study drug) and additionally for study drug-related TEAEs (as defined above). All AE summary tables will include the number (%) of subjects reporting at least one AE and the number of AEs in each part/treatment and overall.

The number of TEAEs and the number and % of subjects reporting at least 1 TEAE will be tabulated by system organ class (SOC) and preferred term (PT). A subject reporting multiple episodes of a particular AE will only contribute 1 count towards the corresponding SOC and PT (*Table 14.3.1.3, 14.3.1.4*). This summary will also be repeated for serious TEAEs (*Table 14.3.153, 14.3.1.6*), [redacted] (*Table 14.3.1.7, 14.3.1.8*) and post-treatment TEAEs (*Table 14.3.1.9*).

For each SOC and PT, the number and % of subjects reporting TEAEs will be tabulated by maximum severity and strongest relationship to study drug. For the summary of TEAEs by severity, if a subject has multiple events occurring within the same SOC or PT the event with the highest severity will be counted (*Table 14.3.1.10, 14.3.1.11*). Similarly, for TEAEs by relationship to treatment, if a subject has multiple events occurring within the same SOC or PT, the event with the highest association to study drug will be counted (presented for all TEAEs only, i.e. not replicated for study drug-related TEAEs) (*Table 14.3.1.12*).

For the most frequently reported TEAEs (defined as AEs reported by ≥ 5% of subjects within a treatment), the number of TEAEs and the number and % of subjects reporting at least 1 TEAE will be tabulated by PT, sorted in descending frequency by the number of subjects (*Table 14.3.1.13, 14.3.1.14*). Following determination of the most frequently reported TEAEs, a subset will be presented for [redacted] (*Table 14.3.1.15, 14.3.1.16*).

The number of TEAEs and the number and % of subjects reporting at least 1 TEAE will be tabulated by SOC, PT and day of onset relative to treatment period (*Table 14.3.1.17, 14.3.1.18*). A subject reporting multiple episodes of a particular AE will only contribute 1 count towards the corresponding onset day, SOC and PT.

Relative day of onset will be calculated as:

- If AE onset date is greater than or equal to date of study drug intake then relative day of onset = AE onset date – date of dose (of the associated study part/treatment) + 1.
- If AE onset date is less than date of first study drug intake at Visit 2 (Part 1), then relative day of onset = AE onset date – date of first study drug intake.

Relative day of onset will not be calculated where there are partial/missing dates of AE onset.

The derived variable 'Duration' should be presented where full date and time are present. If partial dates are present for any parameter required in the calculation, then the variable will not be populated.

AE duration will be presented in the format *dd:hh:mm* and calculated as:

- When AE is resolved, (Date/Time of Resolution - Date/Time of Onset) + 1 minute;
- When AE is not resolved by the end of the trial, AE duration = Date of completion/discontinuation – AE onset date + 1. In this case the duration will be presented as ">x days" in the listings.

The following will be presented in listing format within the data summaries:

- Serious Adverse Events – If there are none present then the listing will be produced stating: 'No subjects experienced any serious adverse events.' (*Table 14.3.1.19*).
- Adverse Events which Led to Withdrawal – If there are none present then the listing will be produced stating: 'No subjects experienced any adverse events that led to withdrawal.' (*Table 14.3.1.20*).
- Deaths – If there are none present then the listing will be produced stating: 'No subjects experienced any fatal adverse events.' (*Table 14.3.1.21*).

All AEs recorded on the eCRF will be presented within the data listings (*Listing 16.2.7.1*). AE listings will be presented by study part and treatment phase (i.e. 'Prior to dosing', 'On-treatment' (assigned to treatment) or 'Post-treatment' (assigned to treatment)).

AEs will be listed and summarised using the Safety Set.

11.6.2 Laboratory Data

Routine clinical laboratory tests will be carried out at Visit 1 (Screening), Visit 2 (at approx. 4 h post dose), Visit 3 and Visit 4.

The planned hematology, clinical chemistry, coagulation and urinalysis parameters are listed in section 9.2.1.

Laboratory data listings will be presented in two ways:

- Out of range values - any values that fall outside of the normal/alert ranges based on the reference ranges provided by the central laboratory or local laboratory, as appropriate (presented in listing format within the data summaries) (*Table 14.3.2.1 - 14.3.2.4*).

- All laboratory data including change from baseline results at each visit and the physician's review (Normal, Abnormal-NCS, Abnormal-CS)) with any out of range values flagged (presented within the data listings) (*Listing 16.2.8.1 – 16.2.8.4*).

Descriptive statistics (N, n, mean, SD, minimum, median and maximum) for absolute and change from baseline (last assessment prior to dosing at Visit 2) values at each visit will be tabulated by study part and treatment for hematology, clinical chemistry and coagulation results (*Table 14.3.2.5, 14.3.2.6, 14.3.2.7*). Urinalysis results at each visit will be summarised using frequencies (n, %) by study part and treatment (*Table 14.3.2.8*).

Shift tables from baseline for hematology, clinical chemistry, coagulation and urinalysis parameters will be produced. The 4x4 cross tabulations (from missing/low/normal/high to missing/low/normal/high based on out of range flags) will be presented by study part and treatment (*Table 14.3.2.9 - 14.3.2.12*).

Serum and urine pregnancy test results and any unplanned laboratory parameters will also be listed (*Listing 16.2.4.6, 16.2.8.5*). If there are no further parameters databased other than those specified in section 9.2.1 then the 'Other Laboratory Data' listings should display, 'No other laboratory parameters to report'.

Laboratory data will be listed and summarised using the Safety Set. Any Visit 3 or Visit 4 occurring outside the 7 days post-dose visit window will be flagged within the listing.

11.6.3 Vital Signs

Supine systolic and diastolic blood pressure and pulse rate, respiration rate and body temperature will be recorded at Visit 1; at pre-dose (0 h), 1 h and 4 h post-dose during Visit 2; at Visit 3 and Visit 4.

Absolute and change from baseline (last assessment prior to dosing at Visit 2) vital signs results will be listed with any out of normal range values (see Appendix 16.2) flagged (flag 'H' or 'L' appended to relevant result) (*Listing 16.2.9.1, 16.2.9.2*). Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline results at each visit/time point will be tabulated by study part and treatment (*Table 14.3.3.1*).

Vital signs data will be listed and summarised using the Safety Set. Any Visit 3 or Visit 4 occurring outside the 7 days post-dose visit window will be flagged within the listing.

11.6.4 Physical Examination

A physical examination will be conducted at Visit 1, Visit 2 (if clinically indicated), Visit 3 and Visit 4.

Physical examination results will be listed using the Safety Set (*Listing 16.2.10.1*). Any Visit 3 or Visit 4 occurring outside the 7 days post-dose visit window will be flagged within the listing.

11.6.5 Electrocardiogram

A 12-lead ECG will be completed at Visit 1; at pre-dose and 1 h post-dose during Visit 2; at Visit 3 and Visit 4.

Absolute and change from baseline (last assessment prior to dosing at Visit 2) 12-lead ECG parameters (heart rate, PR interval, RR interval, QRS width, QT interval and QTcF interval) will be listed with any out of normal range values (see Appendix 16.2) flagged (flag 'H' or 'L' appended to relevant result) (*Listing 16.2.11.1, 16.2.11.2*). Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline values at each visit/time point will be tabulated by study part and treatment (*Table 14.3.4.1*).

Shift tables from baseline for ECG interpretation will be presented. The 3x3 cross tabulations (from Normal/Abnormal NCS/Abnormal CS to Normal/Abnormal NCS/Abnormal CS) will be presented by study part and treatment (*Table 14.3.4.2*).

ECG data will be listed and summarised using the Safety Set. Any Visit 3 or Visit 4 occurring outside the 7 days post-dose visit window will be flagged within the listing.

11.7 Study Drug Exposure and Compliance

Study drug in Part 1 of the study will be administered under the direct supervision of the site staff and hence compliance is not expected to be problematic. Compliance in Part 2 of the study will be assessed by review of the returned study drug and subject diaries.

Part 1 Compliance = (Number of tablets administered at Visit 2 / 6) * 100, where 6 is the number of tablets expected to be used.

Part 2 Compliance = ([number of tablets dispensed at visit – number of tablets returned at next visit] / 6) x 100.

Dose administration and subject diary, dispensing and return information will be listed (*Listing 16.2.1.6, 16.2.1.7*). Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of treatment compliance will be tabulated by treatment along with frequencies (n, %) of the number of subjects fully compliant (*Table 14.6.1.5*).

11.8 Prior and Concomitant Medication

All medications, therapies and supplements taken by subjects within 93 days prior to Visit 1 (Screening) until the end of study will be recorded in the eCRF. Medications will be classified using the World Health Organisation Drug Dictionary (WHO-DDE) version 2018. The Anatomical Therapeutic Chemical (ATC) Classification and WHO-DRUG PT will be used to list and summarise the data.

A medication will be assigned to the most recent treatment if it starts within 48 hours after the corresponding dose. Where there are only partial dates/times recorded for a medication, the medication will be assigned to treatment if it cannot be ruled out based on the partial information and flagged within the data listing.

A medication will be regarded as prior if it stops prior to administration of first treatment at Visit 2. The treatment phase will be presented as 'Prior to Treatment'. For any medication that started prior to first

administration of study drug at Visit 2 but is ongoing following administration of study drug, the treatment phase will be described as 'Prior and Ongoing'. Any medication starting after first administration of study drug at Visit 2 until the end of study will be defined as concomitant (treatment phase 'Concomitant'). Concomitant medications which are taken within 48h following study drug administration will also be presented separately.

Prior, ongoing, concomitant and concomitant medication taken within 48h following study drug administration will be listed (*Listing 16.2.12.1 – 16.2.12.4*). The number (%) of subjects reporting the use of any prior, prior and ongoing and concomitant medications and the number (%) of subjects taking each drug by ATC classification level 4 and preferred term will be summarised by sequence group and overall (*Table 14.6.1.1, 14.6.1.2, 14.6.1.3*). The number (%) of subjects reporting the use of concomitant medications within 48h following study drug administration and the number (%) of subjects taking each drug by ATC classification level 4 and preferred term will be summarised by part/treatment and overall (*Table 14.6.1.4*).

Prior and concomitant medications will be listed and summarised using the Safety Set.

11.9 All Other Data

All other data will be listed using the Safety Set, including the following: Visit Dates, Informed Consent, Conventional Attack Treatment Administration, Female Obstetric History, Inclusion/Exclusion Criteria Failures, Pharmacodynamic Blood Sampling Times, Follow-Up Telephone Call, Procedures and Non-Drug Therapies.

12 VALIDATION

All tables, figures and listings will be subject to independent quality control and visual review. Unique tables will be independently programmed. QC findings will be documented in an Output Summary file quality control form and actions taken will also be documented.

The completed form will be reviewed and signed by the statistical programmers and the study statistician.

13 LITERATURE CITATIONS/REFERENCES

14 LIST OF TABLES, FIGURES AND LISTINGS

List of Tables and Figures Contained in Report Section 14

***** indicates topline TFLs**

14.1 Disposition and Demographic Data

14.1.1 Disposition Data

14.1.2 Demographic Data and Baseline Characteristics

14.2 Efficacy Data

14.2.1 Primary Efficacy Endpoint

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14.2.2 Secondary Efficacy Endpoints

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Table 14.2.2.2	Summary of Change in HAE Attack Severity on the PGI-C by Time Point with Assessments Post-Conventional Attack Treatment Excluded	Full Analysis Set
Table 14.2.2.3	Summary of Worsening in HAE Attack Severity on the PGI-S by One Level or More by Time Point with Assessments Post-Conventional Attack Treatment Excluded	Full Analysis Set
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Table 14.2.2.8	Descriptive Statistics of Absolute and Change from Baseline HAE Attack VAS Scores with Assessments Post-Conventional Attack Treatment Excluded	Full Analysis Set
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Table 14.2.2.13	Descriptive Statistics of Absolute and Change from Baseline HAE Attack Index VAS Score with Missing Values and Assessments Post-Conventional Attack Treatment Imputed using LOCF	Full Analysis Set
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Table 14.2.2.14	Analysis of Time to either Worsening in HAE Attack Severity by One Level or More on the PGI-S or Conventional Attack Treatment Use within 12h of Study Drug ***	Full Analysis Set
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Table 14.2.2.20	*Summary of Worsening in HAE Attack Severity on the PGI-S by One Level or More by Time Point with Assessments Post-Conventional Attack Treatment Excluded – (if required)*	*Per Protocol Set*

Table 14.2.2.21	*Descriptive Statistics of Absolute and Change from Baseline HAE Attack Severity on the PGI-S with Assessments Post-Conventional Attack Treatment Excluded – (if required)*	*Per Protocol Set*
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Table 14.2.2.46	*Descriptive Statistics of Absolute and Change from Baseline HAE Attack Index VAS Score with Assessments Post-Conventional Attack Treatment Excluded – (if required)*	*Safety Set*
Figure 14.2.2.57	*Mean HAE Attack Index VAS Score with Assessments Post-Conventional Attack Treatment Excluded – (if required)*	*Safety Set*
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Table 14.2.2.47	*Descriptive Statistics of Absolute and Change from Baseline HAE Attack Index VAS Score with Missing Values and Assessments Post-Conventional Attack Treatment Imputed using LOCF – (if required)*	*Safety Set*
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Table 14.2.2.48	*Analysis of Time to either Worsening in HAE Attack Severity by One Level or More on the PGI-S or Conventional Attack Treatment Use within 12h of Study Drug – (if required)*	*Safety Set*
Figure 14.2.2.61	*Survival Plot of Time to either Worsening in HAE Attack Severity S by One Level or More on the PGI-S or Conventional Attack Treatment Use within 12h of Study Drug – (if required)*	*Safety Set*
Table 14.2.2.49	*Analysis of Proportion of HAE Attacks that Worsen in Severity by One Level or More on the PGI-S or Require Conventional Attack Treatment within 12h of Study Drug – (if required)*	*Safety Set*
Table 14.2.2.50	*Analysis of Time to Symptom Relief defined as HAE Attack Rated as a Little Better or Higher on the PGI-c for Two Consecutive Time Points within 12h of Study Drug – (if required)*	*Safety Set*
Figure 14.2.2.62	*Survival Plot of Symptom Relief defined as HAE Attack Rated as a Little Better or Higher on the PGI-c for Two Consecutive Time Points within 12h of Study Drug – (if required)*	*Safety Set*
Table 14.2.2.51	*Analysis of Time to Symptom Relief defined as 50% Reduction in Composite VAS Score for Three Consecutive Time Points within 12h of Study Drug – (if required)*	*Safety Set*
Figure 14.2.2.63	*Survival Plot of Time to Symptom Relief defined as 50% Reduction in Composite VAS Score for Three Consecutive Time Points within 12h of Study Drug – (if required)*	*Safety Set*

14.2.3 Exploratory Efficacy Endpoints

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Table 14.2.3.2	Analysis of Time to Use of Conventional Attack Treatment within 24h of Study Drug ***	Full Analysis Set
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Table 14.2.3.4	Analysis of Cumulative HAE Attack Severity on the PGI-S expressed as AUC within 12h and 24h of Study Drug ***	Full Analysis Set
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Table 14.2.3.6	Analysis of Time to either Worsening in HAE Attack Severity by One Level or More on the PGI-S or Conventional Attack Treatment Use within 24h of Study Drug	Full Analysis Set
Figure 14.2.3.2	Survival Plot of Time to either Worsening in HAE Attack Severity by One Level or More on the PGI-S or Conventional Attack Treatment Use within 24h of Study Drug	Full Analysis Set
Table 14.2.3.7	Analysis of Time to Worsening in HAE Attack Severity by One Level or More on the PGI-S within 12h and 24h of Study Drug	Full Analysis Set
Figure 14.2.3.3	Survival Plot of Time to Worsening in HAE Attack Severity by One Level or More on the PGI-S within 12h and 24h of Study Drug	Full Analysis Set
Table 14.2.3.8	Analysis of Proportion of HAE Attacks that Improve in Severity by One Level or More on the PGI-S within 12h and 24h of Study Drug	Full Analysis Set
Table 14.2.3.9	Analysis of Time to Improvement in HAE Attack Severity by One Level or More on the PGI-S within 12h and 24h of Study Drug	Full Analysis Set
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Table 14.2.3.12	Analysis of Proportion of HAE Attacks that are Stable or Impoved in Severity on the PGI-S within 12h and 24h of Study Drug	Full Analysis Set
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Table 14.2.3.25	Analysis of Proportion of HAE Attacks with Symptom Relief defined as 50% Reduction in Composite VAS Score for Three Consecutive Time Points within 24h of Study Drug	Full Analysis Set
Table 14.2.3.26	Analysis of Time to Symptom Relief defined as 50% Reduction in Composite VAS Score for Three Consecutive Time Points within 24h of Study Drug	Full Analysis Set
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14.3 Safety Data

14.3.1 Adverse Events

Table 14.3.1.1	Treatment-Emergent Adverse Events	Safety Set
Table 14.3.1.2	On-Treatment Treatment-Emergent Adverse Events	Safety Set
Table 14.3.1.3	Treatment-Emergent Adverse Events by SOC and PT	Safety Set
Table 14.3.1.4	Study Drug-Related Treatment-Emergent Adverse Events by SOC and PT	Safety Set
Table 14.3.1.5	Serious Treatment-Emergent Adverse Events by SOC and PT	Safety Set
Table 14.3.1.6	Serious Study Drug-Related Treatment-Emergent Adverse Events by SOC and PT	Safety Set
Table 14.3.1.7	On-Treatment Treatment-Emergent Adverse Events by SOC and PT	Safety Set
Table 14.3.1.8	On-Treatment Study Drug-Related Treatment-Emergent Adverse Events by SOC and PT ***	Safety Set
Table 14.3.1.9	Post-Treatment Treatment-Emergent Adverse Events by SOC and PT	Safety Set
Table 14.3.1.10	Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity	Safety Set
Table 14.3.1.11	Study Drug-Related Treatment-Emergent Adverse Events by SOC, PT and Maximum Severity	Safety Set

14.3.1 Adverse Events

Table 14.3.1.12	Treatment-Emergent Adverse Events by SOC, PT and Strongest Relationship to Study Drug	Safety Set
Table 14.3.1.13	Most Frequent Treatment-Emergent Adverse Events by PT	Safety Set
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Table 14.3.1.15	Most Frequent On-Treatment Treatment-Emergent Adverse Events by PT	Safety Set
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Table 14.3.1.17	Treatment-Emergent Adverse Events by SOC, PT and Day of Onset	Safety Set
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Table 14.3.1.19	Listing of Serious Adverse Events	Safety Set
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14.3.2 Laboratory Safety

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Table 14.3.2.2	Clinical Chemistry Out of Normal Range Data	Safety Set
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Table 14.3.2.4	Urinalysis Out of Normal Range Data	Safety Set
Table 14.3.2.5	Summary of Absolute and Change from Baseline Hematology Data	Safety Set
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Table 14.3.2.8	Summary of Urinalysis Data	Safety Set
Table 14.3.2.9	Shift Table of Hematology Parameters	Safety Set
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Table 14.3.2.11	Shift Table of Coagulation Parameters	Safety Set
Table 14.3.2.12	Shift Table of Urinalysis Parameters	Safety Set

14.3.3 Vital Signs

Table 14.3.3.1	Summary of Absolute and Change from Baseline Vital Signs Data	Safety Set

14.3.4 ECG

Table 14.3.4.1	Summary of Absolute and Change from Baseline 12-lead ECG Data	Safety Set
Table 14.3.4.2	Shift Table of 12-lead ECG	Safety Set

14.4 Pharmacokinetics

14.4.1 Concentration Data

Table 14.4.1.1	Summary of Plasma KVD900 Concentration Data	PK Set
Figure 14.4.1.1	Geometric Mean Plasma KVD900 Concentration-Time Curves on a Linear Scale	PK Set
Figure 14.4.1.2	Geometric Mean Plasma KVD900 Concentration-Time Curves on a Semi-Logarithmic Scale	PK Set

14.4.2 Derived Pharmacokinetics

Table 14.4.2.1	Summary of Derived Plasma KVD900 Pharmacokinetic Parameters	PK Set

14.5 Pharmacodynamics

Not applicable.

14.6 Other

14.6.1 Other

Table 14.6.1.1	Summary of Prior Medications	Safety Set
Table 14.6.1.2	Summary of Prior and Ongoing Medication	Safety Set
Table 14.6.1.3	Summary of Concomitant Medication	Safety Set
Table 14.6.1.4	Summary of Concomitant Medication Taken Within 48h Following Study Drug	Safety Set
Table 14.6.1.5	Summary of Study Drug Exposure and Compliance	Safety Set

Subject Data: Listings Contained in Report Appendix 16.2

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Listing 16.2.1.2	Screening Completion	All Enrolled Subjects
Listing 16.2.1.3	Final Status	Safety Set
Listing 16.2.1.4	Discontinued Subjects	Safety Set
Listing 16.2.1.5	Visit Dates	Safety Set
Listing 16.2.1.6	Diary, Study Drug Dispensing and Return	Safety Set
Listing 16.2.1.7	Study Drug Administration	Safety Set
Listing 16.2.1.8	Conventional Attack Treatment Administration	Safety Set

16.2.2 Protocol Deviations

Listing 16.2.2.1	Protocol Deviations	Safety Set

16.2.3 Analysis Sets

Listing 16.2.3.1	Analysis Sets	All Randomised Subjects

16.2.4 Demographic Data and Other Baseline Characteristics

Listing 16.2.4.1	Demographic Information	Safety Set
Listing 16.2.4.2	Medical History and Concurrent Conditions	Safety Set
Listing 16.2.4.3	HAE History	Safety Set
Listing 16.2.4.4	Recent HAE Attack Profile	Safety Set
Listing 16.2.4.5	Female Obstetric History	Safety Set
Listing 16.2.4.6	Pregnancy Test	Safety Set
Listing 16.2.4.7	Inclusion/Exclusion Criteria Failures	Safety Set

16.2.5 Drug Concentration Data and Pharmacokinetics

16.2.5 Drug Concentration Data and Pharmacokinetics

Listing 16.2.5.1	Plasma KVD900 Concentration Data	Safety Set
Figure 16.2.5.1	Individual Plasma KVD900 Concentration-Time Curves on a Linear Scale	Safety Set
Figure 16.2.5.2	Individual Plasma KVD900 Concentration-Time Curves on a Semi-Logarithmic Scale	Safety Set
Listing 16.2.5.2	Individual Derived Plasma KVD900 Pharmacokinetic Parameters	Safety Set

16.2.6 Efficacy

16.2.6 Efficacy

Listing 16.2.6.1	HAE Attack Onset	Safety Set
Listing 16.2.6.2	HAE Attack Monitoring	Safety Set
Listing 16.2.6.3	Efficacy Response Data	Safety Set
Listing 16.2.6.4	HAE Attack Severity on the PGI-S AUCs	Safety Set
Listing 16.2.6.5	HAE Attack Severity on the PGI-C AUCs	Safety Set
Listing 16.2.6.6	HAE Attack Symptom Composite VAS Score AUCs	Safety Set

16.2.7 Adverse Events

Listing 16.2.7.1	Adverse Events	Safety Set

16.2.8 Individual Laboratory Safety Measurements

Listing 16.2.8.1	Hematology Data	Safety Set
Listing 16.2.8.2	Clinical Chemistry Data	Safety Set
Listing 16.2.8.3	Coagulation Data	Safety Set
Listing 16.2.8.4	Urinalysis Data	Safety Set
Listing 16.2.8.5	Other Laboratory Data	Safety Set

16.2.9 Vital Signs

Listing 16.2.9.1	Vital Signs Data	Safety Set
Listing 16.2.9.2	Vital Signs Change from Baseline	Safety Set

16.2.10 Physical Examination

Listing 16.2.10.1	Physical Examination Data	Safety Set

16.2.11.3 ECG

Listing 16.2.11.1	12-lead ECG Data	Safety Set
Listing 16.2.11.2	12-lead ECG Change from Baseline	Safety Set

16.2.12	Prior and Concomitant Medication	
Listing 16.2.12.1	Prior Medications	Safety Set
Listing 16.2.12.2	Prior and Ongoing Medications	Safety Set
Listing 16.2.12.3	Concomitant Medications	Safety Set
Listing 16.2.12.4	Concomitant Medications Taken within 48h Following Study Drug	Safety Set

16.2.13 Pharmacodynamics

16.2.13	Pharmacodynamic Data	
Listing 16.2.13.1	Pharmacodynamic Blood Sampling Times	Safety Set

16.2.14 Other

16.2.14	Other Data	
Listing 16.2.14.1	Procedures and Non-Drug Therapies	Safety Set
Listing 16.2.14.2	Follow-Up Telephone Call	Safety Set

15 SHELLS FOR TABLES, FIGURES AND LISTINGS

The intended layouts for tables, figures and listings are presented. However, it may be appropriate to change the layouts, upon review of the data available, for completeness and clarity.

QCd output will be produced as Rich Text Format (.rtf) files for convenient inclusion in the CSR.

The default tables, figures and listings (TFL) layout will be as follows:

Orientation	A4 Landscape
Margins	Top: 2.54 cm Bottom: 2.54 cm Left: 2.54 cm Right: 2.54 cm
Font	Courier New 9pt
Headers (Centre)	Sponsor Protocol Number, TFL Number, Title, Analysis Set
Footers (Left)	Source Listing, Date/Time TFL Generated, Page Number, i.e. Page x of y

Listing shells are displayed within this document without the comments field but, should there be any comments recorded for the represented data, this field will be added to the listing. In addition, at the time of programming, footnotes will be added to the listing, table or figure as needed. All footnotes will be used for purposes of clarifying the presentation.

Should the number of variables within a listing or table be too great to fit on one page without compromising clarity, then the variables will be split across multiple subsequent pages and key identifying variables replicated with these (i.e. subject number, visit etc). The differing pages will be identified using a sequential number which will follow the TFL title, i.e. xxxx - (1), xxxx - (2).

All final TFLs will be reported from SDTM and ADaM datasets. SDTM and ADaM details will be documented in a separate specification document.

16 APPENDICES

16.1 STUDY FLOW CHART

	Screening	Part 1	Part 2			End of Study/ED*
Clinic Visit (V)	**Visit 1**	**Visit 2***	**1st eligible# HAE attack**	**Visit 3***	**2nd eligible# HAE attack**	**Visit 4***
Informed Consent	X					
Eligibility Assessment	X	X				
Medical History[a]	X					
Demographics[b]	X					
Physical Examination[c]	X	(X)[c]		X		X
Vital Signs[d]	X	X[a]		X		X
Electrocardiogram[n]	X	X[n]		X		X
Safety Laboratory[e]	X	X[e]		X		X
Pregnancy Test[f]	X serum	X[f] serum & urine		X serum		X serum
Concomitant Medications	X	X		X		X
Adverse Events[g]	X	X		X		X
Randomize subject		X				
Subject Diary completion training, dispensing and return		X		X		X[j]
C1INH / icatibant washout check[k]		X	X		X	
Dose[l]		X	X		X	
PK / PD samples[h]		X				
Study drug dispensing and return		X		X		X[j]
Overall attack severity (PGI-S 5LS)[i]			X		X	
Change in attack severity (PGI-C 7TQ)[i]			X		X	
Abdominal pain (VAS)[i]			X		X	
Skin pain (VAS)[i]			X		X	
Skin swelling (VAS)[i]			X		X	
24h telephone follow-up[m]			X		X	

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ED = early discontinuation; HAE = hereditary angioedema; 5LS=5-point Likert scale; 7TQ=7-point transition question; PK = pharmacokinetic; PD = pharmacodynamic; VAS=visual analogue scale;

*Visit 2 to occur within 28 days of Visit 1 (Screening visit).

*Visit 3 to occur as soon as is practicable (within 7 days) following the 1st home-treated HAE attack.

*Visit 4 to occur as soon as is practicable (within 7 days) following the 2nd home-treated HAE attack. Upon subject withdrawal, Visit 4 to be completed as soon as poss ble and, whenever poss ble, prior to starting any new medication or treatment.

When a HAE attack occurs, the subject will telephone the dedicated study physician or qualified designee with a description of the HAE attack documented in the Subject Diary. The dedicated study physician or qualified designee will confirm if the HAE attack is eligible for treatment with the study drug (protocol section 7.2.2.2). If the HAE attack is not elig ble for treatment with the study drug, the subject will commence conventional attack treatment.

[a] 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 93 days [location of the attacks; number of the attacks; maximum severity of the attacks]; 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 93 days, previous participation in interventional clinical studies in the past 93 days.

[b] Demographics: Date of birth; height (meters [m]; without shoes); weight (kilograms [kg]; without shoes or overcoat); race and ethnicity; gender. Calculation of BMI will be automated in the database.

[c] Complete physical examination. Physical examination at Visit 2 if clinically indicated.

[d] Vital signs include pulse rate (PR), respiratory rate (RR), systolic and diastolic blood pressure (SBP, DBP), and body temperature (°C). Visit 2: Vital signs taken pre-dose (0h), 1h, and 4h post-dose.

[e] Laboratory assessments performed by a central laboratory as descr bed in protocol section 6.2.2. Visit 2 labs collected following the 4h post-dose PK collection.

[f] Female subjects of childbearing potential.

- Visit 1: Serum pregnancy test;
- Visit 2: Serum and urine pregnancy test; collected prior to study drug dosing;
- Visit 3: Serum pregnancy test;
- Visit 4: Serum pregnancy test.

[g] AEs recorded from the time of signing of the informed consent form (ICF) up to and including to Visit 4 / ED.

[h] PK / PD samples collected pre-dose (0h), 15 min, 30 min, 45 min, 1h, 1.5h, 2h, 3h, and 4h post-dose.

[i] The subject complete timed assessments of his / her HAE attack symptoms for a 48h period following drug intake as documented in protocol section 6.3.8.

[j] Study drug and Subject Diary return only.

[k] Note: In the event a subject receives treatment with C1INH or icatibant (all doses) during the study, the following washout periods are required prior to the subsequent dosing with study drug:

- 7-day washout period required for C1INH.
- 3-day washout period required for icatibant.

[l] Note: A minimum of 48-hour washout period required between each dose of study drug.

[m] The dedicated study physician or qualified designee will contact the subject within 24h of the eligible HAE attack to confirm the subject's safety and wellbeing.

[n] A 12-lead ECG recorded over at least 10 seconds after the subject has rested supine on a bed for at least 5 min. HR, PR, QRS, QT and RR will be recorded; QTcF calculated as per standard practice.

- Visit 2: ECG performed within 30 min pre-dose and approximately 1h post-dose.

16.2 Normal Ranges

Vital Signs Normal Ranges:

Parameter	Normal Range	Units
Pulse Rate	40-110	Beats per minute (bpm)
Systolic Blood Pressure	90-150	mmHg
Diastolic Blood Pressure	50-90	mmHg
Respiratory Rate	12-18	Breaths per minute
Oral Temperature	35.0-37.5	Degrees Celsius (°C)

12-Lead ECG Normal Ranges:

Parameter	Normal Range	Units
Heart Rate	40-110	Beats per minute (bpm)
PR Interval	120-220	mSec
QRS Duration	70-120	mSec
QT Interval	N/a	N/a
QTc Interval (QTcB=Bazett's, QTcF=Fridericia's)	350-450 males 360-470 females	mSec