



Clinical trial results:

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

Summary

EudraCT number	2021-000136-59
Trial protocol	HU DE IT CZ BG
Global end of trial date	27 October 2022

Results information

Result version number	v1 (current)
This version publication date	29 September 2023
First version publication date	29 September 2023

Trial information

Trial identification

Sponsor protocol code	KVD824-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 152196

Notes:

Sponsors

Sponsor organisation name	KalVista Pharmaceuticals Ltd.
Sponsor organisation address	Porton Science Park, Bybrook Road, Porton Down, Salisbury, United Kingdom, SP4 0BF
Public contact	KalVista Clinical, KalVista Pharmaceuticals Ltd., +44 1980619368, clinical@kalvista.com
Scientific contact	KalVista Clinical, KalVista Pharmaceuticals Ltd., +44 1980619368, clinical@kalvista.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2022
Global end of trial reached?	Yes
Global end of trial date	27 October 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical efficacy of prophylactic treatment with KVD824 compared with placebo in preventing hereditary angioedema (HAE) attacks.

Protection of trial subjects:

The procedures in the clinical trial protocol were designed to ensure that the sponsor and the investigator abided by the principles of the ICH guidelines on GCP E6 (R2), applicable local regulatory requirements, and the Declaration of Helsinki. The clinical trial also followed national and local legal requirements.

Informed consent was obtained from the subjects according to the regulatory and legal requirements of the participating country. The investigator was not to undertake any investigation specifically required for the clinical trial until valid consent had been obtained.

Background therapy:

Conventional care including on-demand treatment for an HAE attack.

Evidence for comparator:

Placebo was used as a comparator.

Actual start date of recruitment	06 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	North Macedonia: 2
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	33
EEA total number of subjects	17

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A sample size of 48 subjects was chosen to evaluate a clinically relevant treatment effect between KVD824 and placebo groups. 33 subjects were randomly assigned to receive the IMP.

Pre-assignment

Screening details:

The screening period included the screening visit and run-in period. After screening, subjects entered into a run-in period of up to 8 weeks in duration. The start of the run-in period was determined by the type of HAE therapy being used by the subject at the time of screening.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	300 mg KVD824 BID

Arm description:

Subjects received 300 mg KVD824 (1 × 300 mg tablet) BID.

Arm type	Experimental
Investigational medicinal product name	KVD824
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 1 × 300 mg tablet KVD824 (TDD of 600 mg). Tablets were to be swallowed whole; tablets were not to be crushed or modified in any way.

Arm title	600 mg KVD824 BID
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Arm description:

Subjects received 600 mg KVD824 (2 × 300 mg tablet) BID.

Arm type	Experimental
Investigational medicinal product name	KVD824
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 × 300 mg tablet KVD824 (TDD of 1200 mg). Tablets were to be swallowed whole; tablets were not to be crushed or modified in any way.

Arm title	900 mg KVD824 BID
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Arm description:

Subjects received 900 mg KVD824 (3 × 300 mg tablet) BID.

Arm type	Experimental
Investigational medicinal product name	KVD824
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 3 × 300 mg tablet KVD824 (TDD of 1800 mg). Tablets were to be swallowed whole; tablets were not to be crushed or modified in any way.

Arm title	Placebo BID
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Arm description:

The placebo group received either 1, 2, or 3 IP matching placebo tablets.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

The placebo group received either 1, 2, or 3 placebo tablets to be consumed BID. Tablets were to be swallowed whole; tablets were not to be crushed or modified in any way.

Number of subjects in period 1^[1]	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID
Started	7	8	7
Completed	5	4	4
Not completed	2	4	3
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	2	2
Trial termination by sponsor	2	2	1

Number of subjects in period 1^[1]	Placebo BID
Started	7
Completed	2
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Trial termination by sponsor	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 33 subjects were assigned to receive treatment. 29 subjects received treatment and are included in safety and efficacy analysis sets.

Baseline characteristics

Reporting groups

Reporting group title	300 mg KVD824 BID
Reporting group description:	
Subjects received 300 mg KVD824 (1 × 300 mg tablet) BID.	
Reporting group title	600 mg KVD824 BID
Reporting group description:	
Subjects received 600 mg KVD824 (2 × 300 mg tablet) BID.	
Reporting group title	900 mg KVD824 BID
Reporting group description:	
Subjects received 900 mg KVD824 (3 × 300 mg tablet) BID.	
Reporting group title	Placebo BID
Reporting group description:	
The placebo group received either 1, 2, or 3 IP matching placebo tablets.	

Reporting group values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID
Number of subjects	7	8	7
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	8	6
From 65-84 years	2	0	1
Age continuous			
Units: years			
median	46.0	44.0	35.0
full range (min-max)	25 to 74	23 to 61	25 to 66
Gender categorical			
Units: Subjects			
Female	6	4	3
Male	1	4	4

Reporting group values	Placebo BID	Total	
Number of subjects	7	29	
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	26	
From 65-84 years	0	3	
Age continuous			
Units: years			
median	53.0		
full range (min-max)	26 to 57	-	
Gender categorical			
Units: Subjects			
Female	3	16	
Male	4	13	

Subject analysis sets

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF (Safety Analysis Set) included all subjects who were randomized and received at least one dose of IMP. Subjects were analyzed according to the actual treatment received.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS (Full Analysis Set) included all subjects who were randomized and received at least one dose of IMP. Subjects were analyzed according to randomized treatment. The FAS population was the population for efficacy analyses.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS (Per-Protocol Set) included all subjects from the FAS who completed at least 28 days of dosing and who did not have predefined major protocol deviations that might have affected the primary efficacy endpoint.

Subject analysis set title	Randomized Set
Subject analysis set type	Full analysis

Subject analysis set description:

Randomized Set included all subjects who are randomized.

Reporting group values	SAF	FAS	PPS
Number of subjects	29	29	23
Age categorical Units: Subjects			
Adults (18-64 years)	26	26	
From 65-84 years	3	3	
Age continuous Units: years			
median	47.0	47.0	
full range (min-max)	23 to 74	23 to 74	
Gender categorical Units: Subjects			
Female	16	16	
Male	13	13	

Reporting group values	Randomized Set		
Number of subjects	33		
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	300 mg KVD824 BID
Reporting group description: Subjects received 300 mg KVD824 (1 × 300 mg tablet) BID.	
Reporting group title	600 mg KVD824 BID
Reporting group description: Subjects received 600 mg KVD824 (2 × 300 mg tablet) BID.	
Reporting group title	900 mg KVD824 BID
Reporting group description: Subjects received 900 mg KVD824 (3 × 300 mg tablet) BID.	
Reporting group title	Placebo BID
Reporting group description: The placebo group received either 1, 2, or 3 IP matching placebo tablets.	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF (Safety Analysis Set) included all subjects who were randomized and received at least one dose of IMP. Subjects were analyzed according to the actual treatment received.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The FAS (Full Analysis Set) included all subjects who were randomized and received at least one dose of IMP. Subjects were analyzed according to randomized treatment. The FAS population was the population for efficacy analyses.	
Subject analysis set title	PPS
Subject analysis set type	Per protocol
Subject analysis set description: The PPS (Per-Protocol Set) included all subjects from the FAS who completed at least 28 days of dosing and who did not have predefined major protocol deviations that might have affected the primary efficacy endpoint.	
Subject analysis set title	Randomized Set
Subject analysis set type	Full analysis
Subject analysis set description: Randomized Set included all subjects who are randomized.	

Primary: Rate of investigator-confirmed HAE attacks during the treatment period

End point title	Rate of investigator-confirmed HAE attacks during the treatment period
End point description: Negative binomial regression on investigator-confirmed HAE attacks while on treatment (FAS) were evaluated. The primary efficacy results should be interpreted with caution acknowledging that an insufficient number of subjects were randomized to achieve adequate power to detect treatment effects between KVD824 and placebo groups.	
End point type	Primary
End point timeframe: During treatment period	

End point values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	7
Units: HAE attacks				
number (confidence interval 95%)				
Estimated HAE attack rate per 4 weeks	1.476 (0.786 to 2.774)	1.072 (0.534 to 2.152)	1.566 (0.814 to 3.012)	2.380 (1.282 to 4.418)

Statistical analyses

Statistical analysis title	Statistical analysis 300 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 300 mg KVD824 BID had Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests were 2-sided with an alpha of 0.0167. The p-values, rates, and rate ratios (95% CI) were from a negative binomial regression model including treatment as a fixed factor, run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, and the logarithm of time each subject was observed 'while on treatment' as an offset.	
Comparison groups	300 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2862
Method	Negative binomial regression model
Parameter estimate	HAE rate ratio (Active vs. Placebo)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.258
upper limit	1.492

Statistical analysis title	Statistical analysis 600 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 600 mg KVD824 BID had Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests were 2-sided with an alpha of 0.0167. The p-values, rates, and rate ratios (95% CI) were from a negative binomial regression model including treatment as a fixed factor, run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, and the logarithm of time each subject was observed 'while on treatment' as an offset.	
Comparison groups	Placebo BID v 600 mg KVD824 BID
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0918
Method	Negative binomial regression model
Parameter estimate	HAE rate ratio (Active vs. Placebo)
Point estimate	0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.178
upper limit	1.138

Statistical analysis title	Statistical analysis 900 mg KVD824 BID
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Statistical analysis description:

Statistical analysis 900 mg KVD824 BID had Bonferroni multiplicity adjustment for multiple dose levels, therefore pairwise comparison tests were 2-sided with an alpha of 0.0167. The p-values, rates, and rate ratios (95% CI) were from a negative binomial regression model including treatment as a fixed factor, run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, and the logarithm of time each subject was observed 'while on treatment' as an offset.

Comparison groups	Placebo BID v 900 mg KVD824 BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3685
Method	Negative binomial regression model
Parameter estimate	HAE rate ratio (Active vs. Placebo)
Point estimate	0.658
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.264
upper limit	1.639

Secondary: Proportion of subjects without investigator-confirmed HAE attacks during the treatment period

End point title	Proportion of subjects without investigator-confirmed HAE attacks during the treatment period
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End point description:

Logistic regression on subjects were measured without investigator-confirmed HAE Attacks (FAS).

End point type	Secondary
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End point timeframe:

During treatment period

End point values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	7
Units: Participants				
Subjects without HAE attack, n	1	2	3	1

Statistical analyses

Statistical analysis title	Statistical analysis 300 mg KVD824 BID
Statistical analysis description: Statistical analysis 300 mg KVD824 BID vs. Placebo was from a logistic regression model including treatment as a fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable.	
Comparison groups	Placebo BID v 300 mg KVD824 BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9798
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	15.6

Statistical analysis title	Statistical analysis 600 mg KVD824 BID
Statistical analysis description: Statistical analysis 600 mg KVD824 BID vs. Placebo was from a logistic regression model including treatment as a fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable.	
Comparison groups	600 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8112
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	17.2

Statistical analysis title	Statistical analysis 900 mg KVD824 BID
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Statistical analysis description:

Statistical analysis 900 mg KVD824 BID vs. Placebo was from a logistic regression model including treatment as a fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable.

Comparison groups	900 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3683
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	36.1

Secondary: Rate of investigator-confirmed HAE attacks that require conventional treatment during the Treatment Period

End point title	Rate of investigator-confirmed HAE attacks that require conventional treatment during the Treatment Period
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End point description:

A summary of negative binomial regression on investigator-confirmed HAE attacks with conventional treatment is presented for the FAS.

End point type	Secondary
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End point timeframe:

During treatment period

End point values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	7
Units: HAE Attacks rate ratio				
number (confidence interval 95%)				
Estimated HAE attack rate per 4 weeks	1.003 (0.461 to 2.183)	1.093 (0.485 to 2.464)	1.229 (0.554 to 2.728)	1.635 (0.754 to 3.548)

Statistical analyses

Statistical analysis title	Statistical analysis 300 mg KVD824 BID
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Statistical analysis description:

Statistical tests were considered exploratory. No multiplicity adjustments were made. The P values were 2-sided with alpha of 0.05. The P values, rates, and rate ratios (95% CI) were from a negative binomial regression model including treatment as a fixed factor, run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, and the logarithm of time each subject was observed 'while on treatment' as an offset.

Comparison groups	300 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3833
Method	Negative binomial regression model
Parameter estimate	HAE rate ratio (Active vs. Placebo)
Point estimate	0.613
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.204
upper limit	1.84

Statistical analysis title	Statistical analysis 600 mg KVD824 BID
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Statistical analysis description:

Statistical tests were considered exploratory. No multiplicity adjustments were made. The P values were 2-sided with alpha of 0.05. The P values, rates, and rate ratios (95% CI) were from a negative binomial regression model including treatment as a fixed factor, run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, and the logarithm of time each subject was observed 'while on treatment' as an offset.

Comparison groups	Placebo BID v 600 mg KVD824 BID
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4819
Method	Negative binomial regression model
Parameter estimate	HAE rate ratio (Active vs. Placebo)
Point estimate	0.668
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.217
upper limit	2.055

Statistical analysis title	Statistical analysis 900 mg KVD824 BID
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Statistical analysis description:

Statistical tests were considered exploratory. No multiplicity adjustments were made. The P values were 2-sided with alpha of 0.05. The P values, rates, and rate ratios (95% CI) were from a negative binomial regression model including treatment as a fixed factor, run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable, and the logarithm of time each subject was observed 'while on treatment' as an offset.

Comparison groups	Placebo BID v 900 mg KVD824 BID
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Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6147
Method	Negative binomial regression model
Parameter estimate	HAE rate ratio (Active vs. Placebo)
Point estimate	0.752
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.248
upper limit	2.282

Secondary: AE-QoL Questionnaire total score and domain scores during the treatment period

End point title	AE-QoL Questionnaire total score and domain scores during the treatment period
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End point description:

Angioedema Quality of Life (AE-QoL) Total Score and domain scores was measured during treatment period.

End point type	Secondary
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End point timeframe:

During treatment period

End point values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	7
Units: Participants				
QoL Functioning Domain Score	7	6	6	4
QoL Fatigue Domain Score	7	6	6	4
QoL Fear Domain Score	7	6	6	4
QoL Nutrition Domain Score	7	6	6	4
QoL Total Score	7	6	6	4

Statistical analyses

Statistical analysis title	Statistical analysis 300 mg KVD824 BID
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Statistical analysis description:

Statistical analysis for QoL Total Score, 300 mg KVD824 BID, were from ANCOVA model with change from baseline to the end of treatment visit as dependent variable, treatment group as main effect, run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates.

Comparison groups	300 mg KVD824 BID v Placebo BID
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Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7676
Method	ANCOVA
Parameter estimate	LS means difference from placebo
Point estimate	3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.74
upper limit	24.96

Statistical analysis title	Statistical analysis 600 mg KVD824 BID
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Statistical analysis description:

Statistical analysis for QoL Total Score, 600 mg KVD824 BID, were from ANCOVA model with change from baseline to the end of treatment visit as dependent variable, treatment group as main effect, run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates.

Comparison groups	600 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4367
Method	ANCOVA
Parameter estimate	LS means difference from placebo
Point estimate	-8.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.59
upper limit	13.82

Statistical analysis title	Statistical analysis 900 mg KVD824 BID
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Statistical analysis description:

Statistical analysis for QoL Total Score, 900 mg KVD824 BID, were from ANCOVA model with change from baseline to the end of treatment visit as dependent variable, treatment group as main effect, run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates.

Comparison groups	900 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	ANCOVA
Parameter estimate	LS means difference from placebo
Point estimate	3.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.42
upper limit	25.77

Secondary: AECT score during the treatment period

End point title	AECT score during the treatment period
End point description:	
A summary of observed values and change from baseline in AECT total score was measured for the FAS. The higher AECT scores indicate a higher level of angioedema control.	
End point type	Secondary
End point timeframe:	
From baseline to EOT visit	

End point values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	7
Units: Participants				
AECT total score change from baseline to EOT visit	7	6	6	4

Statistical analyses

Statistical analysis title	Statistical analysis 300 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 300 mg KVD824 BID was from ANCOVA model with change from baseline to the end of treatment visit as dependant variable, treatment group as main effect, run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates.	
Comparison groups	300 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6224
Method	ANCOVA
Parameter estimate	LS means difference from placebo
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.73
upper limit	7.69

Statistical analysis title	Statistical analysis 600 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 600 mg KVD824 BID was from ANCOVA model with change from baseline to the end of treatment visit as dependant variable, treatment group as main effect, run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates.	
Comparison groups	600 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2506
Method	ANCOVA
Parameter estimate	LS means difference from placebo
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	10.27

Statistical analysis title	Statistical analysis 900 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 900 mg KVD824 BID was from ANCOVA model with change from baseline to the end of treatment visit as dependant variable, treatment group as main effect, run-in period investigator-confirmed HAE attack rate per 4 weeks and baseline value as covariates.	
Comparison groups	900 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9969
Method	ANCOVA
Parameter estimate	LS means difference from placebo
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.44
upper limit	6.47

Secondary: Proportion of subjects with an AECT score ≥ 12 at the end of the treatment period

End point title	Proportion of subjects with an AECT score ≥ 12 at the end of the treatment period
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End point description:

Summary of Logistic Regression on proportion of subjects with AECT Score ≥ 12 was measured at the End of the Treatment Period (FAS).

End point type	Secondary
End point timeframe:	
At the End of the Treatment Period (FAS)	

End point values	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	7
Units: Subjects with AECT score ≥ 12 , n (%)				
Yes	4	5	2	1
No	3	1	4	3
Missing	0	2	1	3

Statistical analyses

Statistical analysis title	Statistical analysis 300 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 300 mg KVD824 BID were from a logistic regression model including treatment as a fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable.	
Comparison groups	300 mg KVD824 BID v Placebo BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3171
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	60.3

Statistical analysis title	Statistical analysis 600 mg KVD824 BID
Statistical analysis description:	
Statistical analysis 600 mg KVD824 BID were from a logistic regression model including treatment as a fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable.	
Comparison groups	Placebo BID v 600 mg KVD824 BID

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0891
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	339.4

Statistical analysis title	Statistical analysis 900 mg KVD824 BID
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Statistical analysis description:

Statistical analysis 900 mg KVD824 BID were from a logistic regression model including treatment as a fixed effect and run-in period investigator-confirmed HAE attack rate per 4 weeks as an adjustment variable.

Comparison groups	Placebo BID v 900 mg KVD824 BID
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7726
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	26

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety analyses were performed by treatment group using the SAF and were presented during treatment period.

Adverse event reporting additional description:

TEAEs in most subjects were mild or moderate in severity. There were no deaths reported in the trial. The trial was terminated due to blinded observation of significant liver enzyme elevations in multiple subjects across dosing groups in the trial.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	300 mg KVD824 BID
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Reporting group description:

Subjects received 300 mg KVD824 (1 × 300 mg tablet) BID.

Reporting group title	600 mg KVD824 BID
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Reporting group description:

Subjects received 600 mg KVD824 (2 × 300 mg tablet) BID.

Reporting group title	900 mg KVD824 BID
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Reporting group description:

Subjects received 900 mg KVD824 (3 × 300 mg tablet) BID.

Reporting group title	Placebo BID
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Reporting group description:

The placebo group received either 1, 2, or 3 IP matching placebo tablets.

Serious adverse events	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic steatosis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis acute			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	300 mg KVD824 BID	600 mg KVD824 BID	900 mg KVD824 BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	6 / 8 (75.00%)	6 / 7 (85.71%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Laryngeal oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Mixed anxiety and depressive disorder			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 8 (12.50%) 1	1 / 7 (14.29%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Liver function test abnormal subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Liver function test increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Weight decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Rib fracture subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Skin laceration			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 8 (25.00%) 2	0 / 7 (0.00%) 0
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	1 / 7 (14.29%) 1
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all) Cholelithiasis subjects affected / exposed occurrences (all) Hepatic cytolysis subjects affected / exposed occurrences (all) Hepatitis acute subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all) Ecchymosis subjects affected / exposed occurrences (all) Hyperkeratosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0

Pruritus subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Skin odour abnormal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Renal and urinary disorders Urine odour abnormal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Musculoskeletal and connective tissue disorders Costochondritis subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 1 / 7 (14.29%) 1	1 / 8 (12.50%) 1 0 / 8 (0.00%) 0	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Pulpitis dental subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1	2 / 8 (25.00%) 2 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0

Viral upper respiratory track infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0

Non-serious adverse events	Placebo BID		
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 7 (14.29%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Hepatic neoplasm subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		
Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Laryngeal oedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		
Psychiatric disorders Mixed anxiety and depressive disorder			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Liver function test abnormal			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Liver function test increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Skin laceration			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all) Cholelithiasis subjects affected / exposed occurrences (all) Hepatic cytolysis subjects affected / exposed occurrences (all) Hepatitis acute subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all) Ecchymosis subjects affected / exposed occurrences (all) Hyperkeratosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		

Pruritus subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Skin odour abnormal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Renal and urinary disorders Urine odour abnormal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Musculoskeletal and connective tissue disorders Costochondritis subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Pulpitis dental subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		

Viral upper respiratory track infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2021	Protocol Version 2.0: • Removed the subject assessment of attack trigger. • Added subject assessment of attack severity. • Clarified that the investigator (or qualified designee) would rate the severity of each attack rather than site staff and removed definitions for the severity ratings. • Provided contact information for Pharmacovigilance for SAE reporting and added that pregnancies would be reported using the pregnancy reporting form using this contact information.
29 March 2021	Protocol Version 3.0: • Clarified that subjects were allowed to receive the COVID-19 vaccination before, during, or after participation in the trial. • Extended number of days permitted between completing the run-in period and the randomization visit from 7 days to 10 days and allowed randomization to occur prior to the randomization visit if the site was dispensing the IMP during the in-clinic randomization visit. • Clarified in exclusion criterion 11 that ongoing participation in an investigational COVID-19 vaccine trial was not allowed within 4 weeks of screening. • Allowed for IMP to be dispensed at the trial site instead of direct shipment to subjects required by local regulations or per the site's local practice. • Provided fax numbers for reporting SAEs. • Removed requirement that subjects had to make reasonable efforts to store IMP at a specific temperature range as IMP was to be stored at room temperature and storage requirements were provided on the label per local regulations. • Clarified that investigators should make every effort possible to follow-up and document the course and outcome of all infants up to 1 year of age born to exposed mothers or born to partners of male subjects. • Clarified when subjects were to begin entering HAE attacks in the eDiary. • Clarified that an investigator must withdraw a subject from the trial if she had a positive pregnancy test during the trial. • Added volume of blood that was to be taken for clinical safety laboratory assessments. • Added clinical safety laboratory hematology tests to match the central laboratory standard panel.
05 May 2021	Protocol Version 4.0: • Incorporated the following additional safety criteria: - Subjects with inadequate organ function were excluded from participation in the trial. - Individual and trial stopping criteria were added. • Excluded use of strong CYP3A4 inhibitors and inducers in the absence of a formal drug-drug interaction trial for KVD824. • Clarified the difference between subject's withdrawal of consent versus subject discontinuation from the trial for other reasons (eg, safety or investigator's discretion). • Clarified that any relevant diseases occurring between the screening visit and the first dose of IMP were to be captured as medical history. • Clarified that clinically significant laboratory abnormalities, as determined by the treating investigator, were to be recorded as AEs after the start of KVD824 dosing.

31 March 2022	Protocol Version 5.0: • Added the trial name of KOMLETE. • Added laboratory assessments at Week 4 to assess liver enzymes in conjunction with the update to the trial stopping criteria in Section 14 of the trial protocol. • Updated the name of the Pharmacovigilance vendor and fax numbers for SAE reporting. • Clarified the following inclusion criteria: - Clarified that C1-INH retesting could occur any time prior to randomization. - Clarified that historical C1-INH functional diagnostic test results for a subject could be used to confirm diagnosis of HAE type I or II in lieu of central or local lab testing. • Clarified that IMP was to be stored at room temperature as labeled. • Added procedural details of RTSM unblinding for investigators if unblinding a subject was needed. • Clarified on the timing of androgen washout period. • Incorporated the following trial stopping criteria: - The occurrence in any subject of a life-threatening SAE not related to HAE. - Liver-related AE that met Hy's Law in more than 1 subject: 1. ALT or AST elevation of $>3 \times \text{ULN}$ 2. TBL elevation of $>2 \times \text{ULN}$ 3. Absence of initial findings of cholestasis (ie, absence of elevation of ALP to $>2 \times \text{ULN}$) 4. No other reason could be found to explain the combination of increased ALT and TBL, such as viral hepatitis A through E; other preexisting or acute liver disease; or another drug capable of causing the observed injury. - Similar grade 3 or higher AE, excluding liver-related AE, in more than 1 subject. • Removed the sentence of "repeat laboratory assessments may be performed" in Section 15.3.4 of the trial protocol. • Clarified timing for the collection of SAE to start at the time of informed consent and to align with other country requirements. • Removed the sentence of "without baseline attack rate as fixed covariate" in Section 18.7 of the trial protocol to correct typographical error. • Added 2 new references.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported