Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-way Crossover Trial to Evaluate the Efficacy and Safety of Two Dose Levels of KVD900, an Oral Plasma Kallikrein Inhibitor, for On-Demand Treatment of Angioedema Attacks in Adolescent and Adult Patients with Hereditary Angioedema Type I or II

Summary

EudraCT number	2021-001226-21
Trial protocol	DE HU GR IT ES NL BG PL PT SK
Global end of trial date	31 December 2023

Results information

Result version number	v1 (current)
This version publication date	07 July 2024
First version publication date	07 July 2024

Trial information

Trial identification

Sponsor protocol code	KVD900-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

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 1980753002, clinicalstudies@kalvista.com
Scientific contact	KalVista Clinical, KalVista Pharmaceuticals Ltd, +44 1980753002, clinicalstudies@kalvista.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002723-PIP01-19
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	03 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical efficacy of KVD900 compared with placebo for the on-demand treatment of HAE attacks.

Protection of trial subjects:

The clinical trial protocol and relevant documents were approved by the EC/IRB and by regulatory authorities.
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 (World Medical Association 2013). The clinical trial also followed national and local legal requirements.
The anonymity of participating patients was maintained. Patients were specified on trial documents by their patient identification number, not by name. Informed consent/assent(s) was obtained from the patient 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/assent had been obtained.

Background therapy:

A total of 107 (97.3%) patients took at least 1 prior medication. The most common prior medications were hematologics taken by 105 (95.5%) patients, other analgesics and antipyretics by 16 patients (14.5%), and antihistamines for systemic use by 15 patients (13.6 %). The most common prior medications by preferred term (taken by ≥10.0% of patients overall) included complement C1 esterase inhibitor (38 [34.5%] patients), conestat alfa (16 [14.5%] patients), icatibant (85 [77.3%] patients), and berotralstat (11 [10%] patients). Patients who entered the trial using long-term prophylactic treatment must be on a stable dose and regimen for at least 3 months prior to the Screening Visit and remained stable during participation in the trial.

Evidence for comparator:

Placebo

Actual start date of recruitment	23 February 2022
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	Netherlands: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	France: 6

Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	North Macedonia: 2
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	136
EEA total number of subjects	56

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)	15
Adults (18-64 years)	117
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were screened at 66 sites in the following countries: Australia (1), Bulgaria (1), Canada (1), France (4), Germany (4), Greece (2), Hungary (1), Israel (4), Italy (2), Japan (6), Netherlands (1), New Zealand (1), North Macedonia (1), Poland (3), Portugal (1), Romania (1), Slovakia (1), Spain (3), UK (5), and USA (23).

Pre-assignment

Screening details:

The trial population included male and female patients 12 years of age and older with a confirmed diagnosis of HAE Type I or II.
The patients comprised 2 subsets: (1) patients who entered the trial taking only conventional on-demand treatment; and (2) patients who entered the trial on a stable dose and regimen of long-term prophylactic treatment.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The trial was performed in a double-blind, double-dummy manner. Only medical emergency allowed unblinding.
136 patients were randomized to treatment by Randomization and Trial Supply Management System. Randomization was stratified by whether the patient entered the trial taking only convention on-demand treatment vs on a stable dose and regimen of long-term prophylactic treatment. Full Analysis Set (FAS) and Safety Analysis Set (SAS) included 110 patients who treated at least 1 attack with IMP.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A

Arm description:

Patients randomized to received treatment in sequence PLB/KVD900 600 mg/KVD900 300 mg.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 2 matching placebo tablets, 600 mg KVD900 (2 × 300 mg KVD900 tablets) or 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet) in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 2 matching placebo tablets, 600 mg KVD900 (2 × 300 mg KVD900 tablets) or 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet) in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second

dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Arm title	Sequence B

Arm description:

Patients randomized to received treatment in sequence PLB/KVD900 300 mg/KVD900 600 mg.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 2 matching placebo tablets, 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), or 600 mg KVD900 (2 × 300 mg KVD900 tablets) in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 2 matching placebo tablets, 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), or 600 mg KVD900 (2 × 300 mg KVD900 tablets) in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Arm title	Sequence C

Arm description:

Patients randomized to received treatment in sequence KVD900 300 mg/KVD900 600 mg/PBL.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), 600 mg KVD900 (2 × 300 mg KVD900 tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), 600 mg KVD900 (2 × 300 mg KVD900 tablets), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours

a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Arm title	Sequence D

Arm description:

Patients randomized to received treatment in sequence KVD900 300 mg/PBL/KVD900 600 mg.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), 2 matching placebo tablets, or 600 mg KVD900 (2 × 300 mg KVD900 tablets), in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), 2 matching placebo tablets, or 600 mg KVD900 (2 × 300 mg KVD900 tablets), in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Arm title	Sequence E

Arm description:

Patients randomized to received treatment in sequence KVD900 600 mg/KVD900 300 mg/PBL.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 600 mg KVD900 (2 × 300 mg KVD900 tablets), 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to self-administer a single dose of 600 mg KVD900 (2 × 300 mg KVD900 tablets), 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet), or 2 matching placebo tablets in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second

dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.

Arm title	Sequence F
Arm description:	
Patients randomized to received treatment in sequence KVD900 600 mg/PBL/KVD900 300 mg.	
Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Patients were to self-administer a single dose of 600 mg KVD900 (2 × 300 mg KVD900 tablets), 2 matching placebo tablets, or 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet) in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Patients were to self-administer a single dose of 600 mg KVD900 (2 × 300 mg KVD900 tablets), 2 matching placebo tablets, or 300 mg KVD900 (1 × 300 mg KVD900 tablet plus 1 placebo tablet) in response to each eligible attack of HAE. If needed (as determined by the patient), after at least 3 hours a second dose of IMP may have been administered for each attack. The second dose of IMP matched the initial dose administered.	

Number of subjects in period 1[1]	Sequence A	Sequence B	Sequence C
Started	18	18	15
Completed	10	14	8
Not completed	8	4	7
Physician decision	-	1	-
Consent withdrawn by subject	-	1	-
Trial termination by Sponsor	7	2	3
Not specified	1	-	2
Lost to follow-up	-	-	1
Protocol deviation	-	-	1

Number of subjects in period 1[1]	Sequence D	Sequence E	Sequence F
Started	17	20	22

Completed	12	8	16
Not completed	5	12	6
Physician decision	-	-	-
Consent withdrawn by subject	-	1	1
Trial termination by Sponsor	5	11	4
Not specified	-	-	-
Lost to follow-up	-	-	1
Protocol deviation	-	-	-

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: A total of 136 patients were randomly assigned to receive the IMP, of which a total of 110 patients treated at least 1 attack with IMP and therefore were included in Full Analysis Set (FAS) and Safety Analysis Set (SAS), and 86 patients were included in Per Protocol Set (PPS). Trial Termination by Sponsor, defined as ongoing patients terminated once the trial objectives were met.

Baseline characteristics

Reporting groups	
Reporting group title	Sequence A
Reporting group description:	
Patients randomized to received treatment in sequence PLB/KVD900 600 mg/KVD900 300 mg.	
Reporting group title	Sequence B
Reporting group description:	
Patients randomized to received treatment in sequence PLB/KVD900 300 mg/KVD900 600 mg.	
Reporting group title	Sequence C
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 300 mg/KVD900 600 mg/PBL.	
Reporting group title	Sequence D
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 300 mg/PBL/KVD900 600 mg.	
Reporting group title	Sequence E
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 600 mg/KVD900 300 mg/PBL.	
Reporting group title	Sequence F
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 600 mg/PBL/KVD900 300 mg.	

Reporting group values	Sequence A	Sequence B	Sequence C
Number of subjects	18	18	15
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	2	2
Adults (18-64 years)	16	15	11
From 65 to 84 years	0	1	2
Age continuous Units: years			
arithmetic mean	37.4	35.8	41.1
standard deviation	± 15.70	± 16.90	± 17.87
Gender categorical Units: Subjects			
Female	13	14	5
Male	5	4	10
Race Units: Subjects			
White	14	18	12
Black or African American	0	0	1
Asian	2	0	1
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Multiple	0	0	0
Not reported	2	0	1
Current Treatment Regimen			

Units: Subjects			
Prophylaxis	3	5	3
On Demand Only	15	13	12
Height (m)			
Units: 1.0			
arithmetic mean	1.646	1.694	1.715
standard deviation	± 0.1216	± 0.1135	± 0.0877
Weight (kg)			
Units: 1.0			
arithmetic mean	75.16	73.88	83.80
standard deviation	± 16.109	± 16.603	± 18.157
Body Mass Index (BMI), (kg/m2)			
Units: 1.0			
arithmetic mean	27.78	25.62	28.62
standard deviation	± 5.638	± 4.743	± 6.603

Reporting group values	Sequence D	Sequence E	Sequence F
Number of subjects	17	20	22
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	2	3	2
Adults (18-64 years)	15	16	20
From 65 to 84 years	0	1	0
Age continuous			
Units: years			
arithmetic mean	31.8	41.4	38.2
standard deviation	± 11.42	± 14.60	± 13.14
Gender categorical			
Units: Subjects			
Female	12	11	11
Male	5	9	11
Race			
Units: Subjects			
White	11	18	19
Black or African American	0	0	0
Asian	5	1	1
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	1
Multiple	0	0	0
Not reported	1	1	1
Current Treatment Regimen			
Units: Subjects			
Prophylaxis	3	3	7
On Demand Only	14	17	15
Height (m)			
Units: 1.0			
arithmetic mean	1.657	1.686	1.704
standard deviation	± 0.1205	± 0.0884	± 0.1126
Weight (kg)			

Units: 1.0			
arithmetic mean	72.28	77.90	83.55
standard deviation	± 23.735	± 16.321	± 21.949
Body Mass Index (BMI), (kg/m2)			
Units: 1.0			
arithmetic mean	26.15	27.37	28.90
standard deviation	± 7.701	± 5.162	± 7.329

Reporting group values	Total		
Number of subjects	110		
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	13		
Adults (18-64 years)	93		
From 65 to 84 years	4		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	66		
Male	44		
Race			
Units: Subjects			
White	92		
Black or African American	1		
Asian	10		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Other	1		
Multiple	0		
Not reported	6		
Current Treatment Regimen			
Units: Subjects			
Prophylaxis	24		
On Demand Only	86		
Height (m)			
Units: 1.0			
arithmetic mean			
standard deviation	-		
Weight (kg)			
Units: 1.0			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI), (kg/m2)			
Units: 1.0			
arithmetic mean			
standard deviation	-		

End points reporting groups

Reporting group title	Sequence A
Reporting group description:	
Patients randomized to received treatment in sequence PLB/KVD900 600 mg/KVD900 300 mg.	
Reporting group title	Sequence B
Reporting group description:	
Patients randomized to received treatment in sequence PLB/KVD900 300 mg/KVD900 600 mg.	
Reporting group title	Sequence C
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 300 mg/KVD900 600 mg/PBL.	
Reporting group title	Sequence D
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 300 mg/PBL/KVD900 600 mg.	
Reporting group title	Sequence E
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 600 mg/KVD900 300 mg/PBL.	
Reporting group title	Sequence F
Reporting group description:	
Patients randomized to received treatment in sequence KVD900 600 mg/PBL/KVD900 300 mg.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included all randomized patients who received trial medication from at least one period for the respective qualifying HAE attack. The Safety Set included all patients who received at least one dose of trial medication.	
Subject analysis set title	300 mg KVD900 - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all randomized patients who received trial medication from at least one period for the respective qualifying HAE attack.	
Subject analysis set title	600 mg KVD900 - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all randomized patients who received trial medication from at least one period for the respective qualifying HAE attack.	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all randomized patients who received trial medication from at least one period for the respective qualifying HAE attack.	

Primary: PGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration

End point title	PGI-C: Time to beginning of symptom relief defined as at least “a little better” (2 time points in a row) within 12 hours of the first IMP administration

End point description:

The analysis of time to the beginning of symptom relief defined as at least "a little better" (2 time points in a row) on the PGI-C within 12 hours of the first IMP administration using the Gehan score transformation test for Full Analysis Set (FAS).
Attacks were treated as right-censored at 12 hours if they did not achieve beginning of symptom relief defined by PGI-C as at least “a little better” (2 time points in a row) or received conventional attack

treatment prior to time-to-event within 12 hours of the first IMP administration.
When an endpoint result was non-evaluable (NE) within 12 hours, if the event did occur, the event must have occurred >12 hours following study drug.

End point type	Primary

End point timeframe:

Within 12 hours of the first investigational medicinal product (IMP) administration.

End point values	300 mg KVD900 - FAS	600 mg KVD900 - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	84	
Units: number				
number (not applicable)				
Number of attacks, events	66	71	41	
Number of attacks, censored	21	22	43	
Median Time to beginning of symptom relief, hours	1.61	1.79	6.72	
Gehan score LS means	-29.44	-11.32	51.59	

Statistical analyses

Statistical analysis title	Gehan score transformation test - 1

Statistical analysis description:

300 mg KVD900 vs Placebo

Comparison groups	300 mg KVD900 - FAS v Placebo - FAS
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear Mixed Model
Parameter estimate	LS means difference from Placebo
Point estimate	-81.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-117.38
upper limit	-44.68

Statistical analysis title	Gehan score transformation test - 2
Comparison groups	600 mg KVD900 - FAS v Placebo - FAS

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Linear Mixed Model
Parameter estimate	LS means difference from Placebo
Point estimate	-62.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-98.61
upper limit	-27.21

Secondary: PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration

End point title	PGI-S: Time to first incidence of decrease from baseline (2 time points in a row) within 12 hours of the first IMP administration

End point description:

Time to the first incidence of decrease from baseline for 2 time points in a row on Patient Global Impression of Severity (PGI-S) within 12 hours of the first IMP administration (i.e., time to reduction in severity) for FAS.
Attacks were treated as right-censored at 12 hours if they did not have a decrease in PGI-S score from baseline for 2 time points in a row or received conventional attack treatment prior to time-to-event within 12 hours of the first IMP administration.
When an endpoint result was non-evaluable (NE) within 12 hours, if the event did occur, the event must have occurred >12 hours following study drug.

End point type	Secondary

End point timeframe:

Within 12 hours of the first IMP administration.

End point values	300 mg KVD900 - FAS	600 mg KVD900 - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	84	
Units: number				
number (not applicable)				
Number of attacks, events	44	49	26	
Number of attacks, censored	43	44	58	
Median (95% CI), hours	9.27	7.75	0	
Gehan score LS means	-38.01	-37.44	13.21	

Statistical analyses

Statistical analysis title	Gehan score transformation test - 1
Comparison groups	300 mg KVD900 - FAS v Placebo - FAS

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036
Method	Linear Mixed Model
Parameter estimate	LS means difference from Placebo
Point estimate	-51.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.13
upper limit	-19.31

Statistical analysis title	Gehan score transformation test - 2
Comparison groups	600 mg KVD900 - FAS v Placebo - FAS
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Linear Mixed Model
Parameter estimate	LS means difference from Placebo
Point estimate	-50.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.82
upper limit	-19.48

Secondary: PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration

End point title	PGI-S: Time to HAE attack resolution defined as "none" within 24 hours of the first IMP administration

End point description:

Time to complete HAE attack resolution on Patient Global Impression of Severity (PGI-S) within 24 hours of the first IMP administration without conventional attack treatment use for FAS.
Attacks were treated as right-censored at 24 hours if they did not have an HAE attack resolution or received conventional attack treatment prior to time-to-event within 24 hours of IMP administration.
When an endpoint result was non-evaluable (NE) within 24 hours, if the event did occur, the event must have occurred >12 hours following study drug.

End point type	Secondary

End point timeframe:

Within 24 hours of the first IMP administration.

End point values	300 mg KVD900 - FAS	600 mg KVD900 - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	87	93	84	
Units: number				
number (not applicable)				
Number of attacks, events	37	46	23	
Number of attacks, censored	50	47	61	
Median (95% CI), hours	0	24.00	0	
Gehan score LS means	1.62	-17.46	56.25	

Statistical analyses

Statistical analysis title	Gehan score transformation test - 1
Comparison groups	300 mg KVD900 - FAS v Placebo - FAS
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Linear Mixed Model
Parameter estimate	LS means difference from Placebo
Point estimate	-54.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.05
upper limit	-22.19

Statistical analysis title	Gehan score transformation test - 2
Comparison groups	600 mg KVD900 - FAS v Placebo - FAS
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear Mixed Model
Parameter estimate	LS means difference from Placebo
Point estimate	-73.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-105.35
upper limit	-42.08

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
On-treatment TEAE was defined as any TEAE occurring within 3 days post-dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	300 mg KVD900 - SAS
Reporting group description:	
The Safety Set included all patients who received at least one dose of trial medication.	
Reporting group title	600 mg KVD900 - SAS
Reporting group description:	
The Safety Set included all patients who received at least one dose of trial medication.	
Reporting group title	Placebo - SAS
Reporting group description:	
The Safety Set included all patients who received at least one dose of trial medication.	

Serious adverse events	300 mg KVD900 - SAS	600 mg KVD900 - SAS	Placebo - SAS
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 86 (1.16%)	2 / 93 (2.15%)	0 / 83 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	0 / 86 (0.00%)	1 / 93 (1.08%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Anisocoria			
subjects affected / exposed	0 / 86 (0.00%)	1 / 93 (1.08%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	1 / 86 (1.16%)	0 / 93 (0.00%)	0 / 83 (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

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

Non-serious adverse events	300 mg KVD900 - SAS	600 mg KVD900 - SAS	Placebo - SAS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 86 (5.81%)	6 / 93 (6.45%)	10 / 83 (12.05%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 86 (0.00%)	3 / 93 (3.23%)	1 / 83 (1.20%)
occurrences (all)	0	3	1
Dizziness			
subjects affected / exposed	0 / 86 (0.00%)	1 / 93 (1.08%)	0 / 83 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 86 (1.16%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 86 (1.16%)	1 / 93 (1.08%)	1 / 83 (1.20%)
occurrences (all)	1	1	1
Nausea			
subjects affected / exposed	0 / 86 (0.00%)	1 / 93 (1.08%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Abdominal pain			

subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 93 (0.00%)	0 / 83 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	1 / 86 (1.16%)	0 / 93 (0.00%)	0 / 83 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Pharyngitis bacterial			
subjects affected / exposed	0 / 86 (0.00%)	0 / 93 (0.00%)	1 / 83 (1.20%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	1 / 86 (1.16%)	0 / 93 (0.00%)	0 / 83 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2022	Protocol Version 2.0. Australia, Bulgaria, Canada, France, Germany, Greece, Hungary, Israel, Italy, Macedonia, Netherlands, New Zealand, Poland, Spain, UK, US.
26 May 2022	Protocol Version 3.0. Australia, Bulgaria, Canada, France, Germany, Greece, Hungary, Israel, Italy, Japan, Macedonia, Netherlands, New Zealand, Poland, Portugal, Romania, Slovakia, Spain, UK, US.
26 April 2023	Protocol Version 4.0. Australia, Bulgaria, Canada, France, Germany, Greece, Hungary, Israel, Italy, Japan, Macedonia, Netherlands, New Zealand, Poland, Portugal, Romania, Slovakia, Spain, UK, US.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported