Clinical trial results:
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

Summary

EudraCT number	2018-004489-32
Trial protocol	GB DE AT HU NL PL IT
Global end of trial date	08 December 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	KVD900-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04208412
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	Vice President, Clinical, KalVista Pharmaceuticals Ltd., +1 857 999 0075, clinical@kalvista.com
Scientific contact	Vice President, Clinical, KalVista Pharmaceuticals Ltd., +44 1980 753002, 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	21 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 December 2020
Global end of trial reached?	Yes
Global end of trial date	08 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

No specific measures to protect participants other than regular monitoring as per Protocol.

The study was conducted in accordance with the principles set forth in the Declaration of Helsinki as amended in 2002, the Guidelines of the International Conference on Harmonisation (ICH) on Good Clinical Practice (GCP) (CPMP/ICH/135/95), as well as the requirements of the European Union Data Protection Directive 95/46/EC, and other applicable regulatory requirements.

Background therapy:

N/A

Evidence for comparator:

N/A; Placebo-controlled study.

Actual start date of recruitment	02 July 2019
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	United States: 6
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	North Macedonia: 3
Worldwide total number of subjects	68
EEA total number of subjects	51

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)	67
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 25-center study in 10 countries.
A total of 68 subjects were entered into Part 1 and subsequently into Part 2, where all 68 subjects were randomized equally to Sequence 1 (600 mg KVD900; Placebo) or Sequence 2 (Placebo; 600 mg KVD900).

Pre-assignment

Screening details:

A total of 84 subjects were enrolled, of which 16 were screen failures.
Main inclusion criteria were: Male or female adult subjects 18 years of age and older with confirmed diagnosis of HAE type I or II and at least 3 documented HAE attacks in the past 93 days. Subjects were required to have adequate organ functions as provided in the Protocol.

Period 1

Period 1 title	Part 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

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

Arms

Arm title	Part 1 - KVD900 600 mg

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	KVD900
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Part 1, subjects received a single dose of 600 mg KVD900 on Visit 2 (within 28 days of screening visit; during the intercritical period between HAE attacks). For clinical study use, KVD900 was formulated as film-coated tablets, KVD900 100 mg Film Coated Tablet.

Number of subjects in period 1	Part 1 - KVD900 600 mg
Started	68
Completed	68

Period 2

Period 2 title	Part 2
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Subjects were randomized on a 1:1 basis to the two sequences for Part 2 (KVD900 600 mg followed by placebo or placebo followed by KVD900 600 mg). The actual treatment sequence for each subject was determined by the randomization scheme. The randomization scheme was produced by a computer software program that incorporated a standard procedure for generating randomization numbers. The randomization scheme informed the Investigator of the kit ID number allocated to the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 2 - Study Arm 1

Arm description:

In Part 2, Sequence 1 (Study Arm 1), subjects received a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects received a single dose of placebo to treat the second eligible HAE attack.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	KVD900
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Part 2, Sequence 1 (Study Arm 1), subjects received a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects received a single dose of placebo to treat the second eligible HAE attack. For clinical study use, KVD900 was formulated as film-coated tablets, KVD900 100 mg Film Coated Tablet.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Part 2, Sequence 1 (Study Arm 1), following resolution of first eligible attack, subjects received a single dose of placebo to treat the second eligible HAE attack. Placebo looked similar to KVD900 100mg film coated tablets.

Arm title	Part 2 - Study Arm 2

Arm description:

In Part 2, Sequence 2 (Study Arm 2) subjects received a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects received a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.

Arm type	Experimental
Investigational medicinal product name	KVD900
Investigational medicinal product code	KVD900
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Part 2 Sequence 2 (Study Arm 2), following resolution of first eligible attack, subjects received a second single dose of 600 mg KVD900 (6 × KVD900 100 mg Film Coated Tablets) to treat the second eligible HAE attack. For clinical study use, KVD900 was formulated as film-coated tablets, KVD900 100 mg Film Coated Tablet.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Part 2, Sequence 2 (Study Arm 2) subjects received a single dose of placebo to treat the first eligible HAE attack.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: A total of 68 subjects entered into Part 1 and subsequently into Part 2 Sequence 1 or 2. Baseline characteristics and demographics were provided for Sequence 1 (Study arm 1 with 34 subjects) and Sequence 2 (Study arm 2 with 34 subjects).

Number of subjects in period 2	Part 2 - Study Arm 1	Part 2 - Study Arm 2
Started	34	34
Completed	25	28
Not completed	9	6
Consent withdrawn by subject	1	-
Other	8	5
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 2 - Study Arm 1
Reporting group description:	
In Part 2, Sequence 1 (Study Arm 1), subjects received a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects received a single dose of placebo to treat the second eligible HAE attack.	
Reporting group title	Part 2 - Study Arm 2
Reporting group description:	
In Part 2, Sequence 2 (Study Arm 2) subjects received a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects received a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.	

Reporting group values	Part 2 - Study Arm 1	Part 2 - Study Arm 2	Total
Number of subjects	34	34	68
Age categorical			
All subjects were White (68 subjects [100%]) and the majority were not Hispanic or Latino (66/68 subjects [97.1%]). Overall, approximately half of the subjects were male (31/68 subjects [45.6%]) and half were female (37/68 [54.4%]). More subjects in Sequence 1 were female (22/34 subjects [64.7%]) and more subjects were male in Sequence 2 (19/34 subjects [55.9%]). There were no notable differences between subjects in Sequence 1 and Sequence 2 in age, height, weight or BMI.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	33	34	67
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	41	35.5	
full range (min-max)	19 to 68	19 to 64	-
Gender categorical			
Units: Subjects			
Female	22	15	37
Male	12	19	31
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	33	33	66
Not reported	1	0	1
Unknown	0	1	1
Race			
Units: Subjects			
White	34	34	68

Height			
Units: meter			
arithmetic mean	1.711	1.730	
full range (min-max)	1.52 to 1.97	1.52 to 1.91	-
Weight			
Units: kilogram(s)			
arithmetic mean	79.89	82.04	
full range (min-max)	48.1 to 122.4	50.1 to 144.6	-
BMI			
Units: kg/m2			
arithmetic mean	27.242	27.336	
full range (min-max)	18.79 to 40.90	20.33 to 40.06	-

End points

End points reporting groups

Reporting group title	Part 1 - KVD900 600 mg
Reporting group description:	
The first dose of study drug was the open label single 600 mg oral dose (6 × KVD900 100 mg Film Coated Tablets) administered in the clinic during Part 1, after completion of all pre–dose assessments.	
Reporting group title	Part 2 - Study Arm 1
Reporting group description:	
In Part 2, Sequence 1 (Study Arm 1), subjects received a single dose of 600 mg KVD900 to treat the first eligible HAE attack. Following resolution of this attack, subjects received a single dose of placebo to treat the second eligible HAE attack.	
Reporting group title	Part 2 - Study Arm 2
Reporting group description:	
In Part 2, Sequence 2 (Study Arm 2) subjects received a single dose of placebo to treat the first eligible HAE attack. Following resolution of this attack, subjects received a second single dose of 600 mg KVD900 to treat the second eligible HAE attack.	
Subject analysis set title	FAS KVD900 600 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who took 600 mg KVD900 in Part 2	
Subject analysis set title	FAS Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who took Placebo in Part 2	

Primary: Time to Conventional Attack Treatment Use within 12 hours of Study Drug

End point title	Time to Conventional Attack Treatment Use within 12 hours of Study Drug
End point description:	
Analysis of time to use of conventional attack treatment within 12 hours of study drug	
End point type	Primary
End point timeframe:	
12 hours	

End point values	FAS KVD900 600 mg	FAS Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: Number of subjects				
Used conventional attack treatment within 12 hours	8	16		
Censored	45	37		

Statistical analyses

Statistical analysis title	Gehan's Generalized Wilcoxon Test
Comparison groups	FAS Placebo v FAS KVD900 600 mg
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [1]
Method	Gehan's Generalized Wilcoxon Test

Notes:

[1] - Gehan's Generalized Wilcoxon Test P-value: KVD900 vs Placebo

Secondary: Worsening of Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS)

End point title	Worsening of Patient Global Impression of Severity (PGI-S) 5-point Likert scale (5LS)

End point description:

Analysis of the Proportion of HAE Attacks that Worsen in Severity by One Level or More on the PGI-S or Require Conventional Attack Treatment within 12 hours of Study Drug; Analysis of time to (1) worsening by one level or more from baseline or (2) use of conventional attack treatment, whichever comes first, within 12 hours of study drug

End point type	Secondary

End point timeframe:

12 hours

End point values	FAS KVD900 600 mg	FAS Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: Number of subjects				
Worsened in severity by 1 or more (Yes)	11	24		
Worsened in severity by 1 or more (No)	42	29		

Statistical analyses

Statistical analysis title	Prescott's Test: KVD900 vs Placebo
Comparison groups	FAS KVD900 600 mg v FAS Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045 [2]
Method	Prescott's Test

Notes:

[2] - Prescott's Test: KVD900 vs Placebo

Statistical analysis title	Gehan's Generalized Wilcoxon Test
Comparison groups	FAS KVD900 600 mg v FAS Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Gehan's Generalized Wilcoxon Test

Notes:

[3] - Gehan's Generalized Wilcoxon Test: 600 mg KVD900 vs Placebo

Secondary: Improvement of Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ)

End point title	Improvement of Patient Global Impression of Change (PGI-C) 7-point transition question (7TQ)

End point description:

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 12 hours of Study Drug

End point type	Secondary

End point timeframe:

12 hours

End point values	FAS KVD900 600 mg	FAS Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: Number of subjects				
HAE attack rated A Little Better or higher	44	27		
Censored	9	26		

Statistical analyses

Statistical analysis title	Gehan's Generalized Wilcoxon Test
Comparison groups	FAS KVD900 600 mg v FAS Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Gehan's Generalized Wilcoxon Test

Notes:

[4] - Gehan's Generalized Wilcoxon Test: 600 mg KVD900 vs Placebo

Secondary: Improvement of Visual Analogue Scale

End point title	Improvement of Visual Analogue Scale

End point description:

Analysis of Time to Symptom Relief defined as 50% Reduction in Composite VAS Score for Three Consecutive Time Points within 12 hours of Study Drug

End point type	Secondary

End point timeframe:

12 hours

End point values	FAS KVD900 600 mg	FAS Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	53		
Units: Number of subjects				
≥ 50% Reduction in Composite VAS Score	33	16		
Censored	20	37		

Statistical analyses

Statistical analysis title	Gehan's Generalized Wilcoxon Test
Comparison groups	FAS KVD900 600 mg v FAS Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Gehan's Generalized Wilcoxon Test

Notes:

[5] - Gehan's Generalized Wilcoxon Test: 600 mg KVD900 vs Placebo

Other pre-specified: Summary of KVD900 Plasma Concentration Data (PK Set)

End point title	Summary of KVD900 Plasma Concentration Data (PK Set)

End point description:

KVD900 was rapidly absorbed following oral administration, with measurable concentrations detected within 0.25 hours. Following treatment with 600 mg KVD900, mean plasma KVD900 concentration increased from 1710 ng/mL (SD: 2340 ng/mL) at 0.25 hours to a peak of 4920 ng/mL (SD: 3070 ng/mL) at 0.75 hours. Peak median plasma KVD900 concentration was also at 0.75 hours (4690 ng/mL [range: 50.0 to 13600 ng/mL]). Following treatment with 600 mg KVD900, geometric mean plasma KVD900 concentration increased from 501 ng/mL at 0.25 hours to a peak of 4020 ng/mL at 1.5 hours.

End point type	Other pre-specified

End point timeframe:

Samples for pharmacokinetic evaluation of Cmax in all were obtained at following timepoints: Pre- Dose and up to 8 samples over a 4 hour period post dose.

End point values	FAS KVD900 600 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax	4920 (± 3070)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs recorded from the time of signing of the informed consent form up to and including to Visit 4/ED	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Part 1 600mg KVD900
Reporting group description: -	
Reporting group title	Part 2 600 mg KVD900
Reporting group description: -	
Reporting group title	Part 2 Placebo
Reporting group description: -	
Reporting group title	KVD900 Combined
Reporting group description: Part 1 and 2 KVD900 combined	

Serious adverse events	Part 1 600mg KVD900	Part 2 600 mg KVD900	Part 2 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)	0 / 58 (0.00%)	0 / 55 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	KVD900 Combined		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Part 1 600mg KVD900	Part 2 600 mg KVD900	Part 2 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 68 (10.29%)	8 / 58 (13.79%)	5 / 55 (9.09%)

Vascular disorders			
Flushing			
subjects affected / exposed	2 / 68 (2.94%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 68 (2.94%)	3 / 58 (5.17%)	1 / 55 (1.82%)
occurrences (all)	2	3	1
Tremor			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Medical device site rash			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 68 (0.00%)	1 / 58 (1.72%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 68 (0.00%)	1 / 58 (1.72%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
Anal incontinence			
subjects affected / exposed	0 / 68 (0.00%)	0 / 58 (0.00%)	1 / 55 (1.82%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 68 (0.00%)	1 / 58 (1.72%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Nausea			

subjects affected / exposed	1 / 68 (1.47%)	2 / 58 (3.45%)	0 / 55 (0.00%)
occurrences (all)	1	2	0
Vomiting			
subjects affected / exposed	0 / 68 (0.00%)	1 / 58 (1.72%)	1 / 55 (1.82%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 68 (0.00%)	1 / 58 (1.72%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 68 (1.47%)	1 / 58 (1.72%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 58 (1.72%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	2 / 55 (3.64%)
occurrences (all)	1	0	2
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 58 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	KVD900 Combined		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 68 (17.65%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	5		
Tremor			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Medical device site rash			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Anal incontinence			
subjects affected / exposed	0 / 68 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Night sweats subjects affected / exposed occurrences (all) Rash erythematous subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1 1 / 68 (1.47%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 2		
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1 1 / 68 (1.47%) 1 1 / 68 (1.47%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2019	Protocol Version 3.0 (dated 16 May 2019; Austria, Czech republic, Germany, Hungary, Italy, Macedonia, Poland, The Netherlands, UK, US)
26 September 2019	Protocol Version 4.0 (dated 26 September 2019; Austria, Czech republic, Germany, Hungary, Italy, Macedonia, Poland, The Netherlands, UK, US)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported