Clinical trial results:
OPuS-2 A multicentre, randomised, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX4161 for 12 weeks as an oral prophylaxis treatment for attacks of hereditary angioedema.

Summary

EudraCT number	2014-002655-26
Trial protocol	GB DE HU BE FR IT
Global end of trial date	08 January 2016

Results information

Result version number	v1 (current)
This version publication date	24 March 2021
First version publication date	24 March 2021

Trial information

Trial identification

Sponsor protocol code	BCX4161-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02303626
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals, Inc
Sponsor organisation address	4505 Emperor Blvd, Suite 200, Durham, United States, 27703
Public contact	Study Director, BioCryst Pharmaceuticals Inc, 001 919-859-1302, clinicaltrials@biocryst.com
Scientific contact	Study Director, BioCryst Pharmaceuticals Inc, 001 919-859-1302, clinicaltrials@biocryst.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	27 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2016
Global end of trial reached?	Yes
Global end of trial date	08 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of prophylactic Avoralstat (BCX4161) 300 mg and 500 mg administered three times daily for 12 weeks compared to placebo

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, and in accordance with the Declaration of Helsinki. The informed consent form (ICF), protocol and amendments for this trial were submitted to and approved by an appropriate Independent Ethics Committee (IEC). Routine monitoring was performed to verify that rights and well-being of subjects were protected. Emergency equipment and medications were available within the clinical unit as per current standard procedures. Any medication considered necessary for the subject's safety and well-being was given at the discretion of the Investigator. A signed informed consent form (ICF) was obtained from each subject prior to performing any study-related procedures. The informed consent process took place under conditions where the subject had adequate time to consider the risks and benefits associated with his/her participation in the study. The Investigator explained to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail.

Background therapy:

Subjects used their prescribed standard of care medication to treat any breakthrough HAE attacks on study

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	110
EEA total number of subjects	50

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)	103
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 110 subjects were randomized/enrolled into 1 of 3 parts.

Pre-assignment

Screening details:

A total of 137 subjects were screened for the study and 110 subjects were randomized and dosed. 27 subjects were screening failures due to one of the following reasons: did not meet inclusion criteria (15), Investigator discretion (1), met exclusion criteria (5), subject consent withdrawn (4), and/or lost to follow-up (2).

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	Investigator, Monitor, Subject

Blinding implementation details:

This was a double-blind study; as such, the treatment assignment in each part was blinded to the PI, study subjects, staff involved in the clinical evaluation of the subjects and the analysis of data, and the Biometrics team.
The PI or designee(s) confirmed subject eligibility.

Arms

Are arms mutually exclusive?	Yes
Arm title	Avoralstat 500mg

Arm description:

5x 100 mg Avoralstat capsules TID

Arm type	Experimental
Investigational medicinal product name	Avoralstat
Investigational medicinal product code	
Other name	BCX4161
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

5 × 100-mg avoralstat capsules for oral administration 3 times per day (total daily dose of 1500 mg) for 12 weeks

Arm title	Avoralstat 300mg

Arm description:

3x 100 mg Avoralstat capsules + 2 matched placebo capsules TID

Arm type	Experimental
Investigational medicinal product name	Avoralstat
Investigational medicinal product code	
Other name	BCX4161
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

3 × 100-mg avoralstat capsules for oral administration 3 times per day (total daily dose of 900 mg) for 12 weeks. At each dose, subjects received 2 placebo capsules together with avoralstat capsules to maintain dose blind.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The matching placebo contained the excipients polyethylene glycol 600, polyethylene glycol 400, alpha tocopherol and Vitamin E-TPGS. Subjects received 2 placebo capsules QID for 12 weeks together with avoralstat capsules to maintain dose blind.

Arm title	Placebo

Arm description:

5x Placebo capsules TID

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The matching placebo contained the excipients polyethylene glycol 600, polyethylene glycol 400, alpha tocopherol and Vitamin E-TPGS. Subjects received 5 capsules, 3 times a day for 12 weeks.

Number of subjects in period 1	Avoralstat 500mg	Avoralstat 300mg	Placebo
Started	38	36	36
Completed	35	35	33
Not completed	3	1	3
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	2	-	-
Pregnancy	-	-	1
Protocol deviation	1	-	-
Lack of efficacy	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	110	110	
Age categorical Units: Subjects			
Adults (18-64 years)	103	103	
From 65-84 years	7	7	
Age continuous Units: years			
arithmetic mean	41.2		
standard deviation	± 13.3	-	
Gender categorical Units: Subjects			
Female	85	85	
Male	25	25	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	2	2	
Black or African American	0	0	
White	102	102	
Other	3	3	
Native Hawaiian or Other Pacific Islander	2	2	
HAE attack rate Units: Subjects			
≥ 1 attack/week	65	65	
< 1 attack/week	45	45	

End points

End points reporting groups

Reporting group title	Avoralstat 500mg
Reporting group description:	
5x 100 mg Avoralstat capsules TID	
Reporting group title	Avoralstat 300mg
Reporting group description:	
3x 100 mg Avoralstat capsules + 2 matched placebo capsules TID	
Reporting group title	Placebo
Reporting group description:	
5x Placebo capsules TID	

Primary: Weekly Rate of Confirmed HAE Attacks

End point title	Weekly Rate of Confirmed HAE Attacks

End point description:

Subjects completed an electronic study diary (e-diary) to record details of all HAE attacks that occurred. Each e-diary recorded HAE attack was reviewed in real-time by the investigator and subjects contacted as needed to discuss any queries or for additional attack details. This information, in conjunction with the e-Diary record, was used by the Investigator to verify or reject the record as an HAE attack. Subject-reported attacks were further adjudicated by the independent Clinical Endpoint Adjudication Panel (CEAP); the CEAP members individually rated each attack as confirmed (C), confirmed with modification (CM) or rejected (R). Attacks confirmed by the adjudication committee were then included in efficacy analyses.

End point type	Primary

End point timeframe:

12 weeks

End point values	Avoralstat 500mg	Avoralstat 300mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	36	
Units: HAE attacks/week				
least squares mean (standard error)	0.589 (± 0.086)	0.675 (± 0.089)	0.593 (± 0.088)	

Statistical analyses

Statistical analysis title	HAE attack rate - 500 mg Avoralstat
Comparison groups	Avoralstat 500mg v Placebo

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.975 [1]
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.248
upper limit	0.24

Notes:

[1] - ANCOVA Model includes terms of treatment and the randomization strata

Statistical analysis title	HAE attack rate - 300 mg Avoralstat
Comparison groups	Placebo v Avoralstat 300mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.512 [2]
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	0.329

Notes:

[2] - ANCOVA Model includes terms of treatment and the randomization strata

Secondary: Number of Attack-Free Days

End point title	Number of Attack-Free Days

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Avoralstat 500mg	Avoralstat 300mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	36	
Units: Attack-Free Days				
least squares mean (standard error)	67.174 (± 2.646)	64.100 (± 2.720)	64.217 (± 2.703)	

Statistical analyses

Statistical analysis title	Attack-Free Days - 500 mg Avoralstat
Comparison groups	Avoralstat 500mg v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.434 [3]
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	2.957
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.153
upper limit	10.427

Notes:

[3] - ANCOVA Model includes terms of treatment and the randomization strata

Statistical analysis title	Attack-Free Days - 300 mg Avoralstat
Comparison groups	Avoralstat 300mg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.976 [4]
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.688
upper limit	7.455

Notes:

[4] - ANCOVA Model includes terms of treatment and the randomization strata

Secondary: HAE Disease Activity

End point title	HAE Disease Activity

End point description:

Disease activity was assessed using an Angioedema Activity Score (AAS) calculated from data entered in the eDiaries by the subject over 84 days. The AAS score was defined as the sum of the individual scores for 4 AAS domains (daily activities, appearance, physical discomfort, and overall severity) for all subject-reported attacks reported during the treatment period. Individual domain scores were based on answers to questions each of which had 4 possible responses scored 0-3 (0 - no impact; 1-3 - increasing levels of impact). The total AAS score per attack could range from 0 to 12; lower scores & higher scores represent lower & higher disease activities, respectively. However, the overall total AAS score reported

for this study included the total scores for all subject-reported attacks, therefore the upper limit of the range was subject-specific. The statistical analysis of the total modified AAS scores for the treatment period is presented below.

End point type	Secondary

End point timeframe:

84 days

End point values	Avoralstat 500mg	Avoralstat 300mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	36	
Units: AAS Score				
least squares mean (standard error)	83.938 (± 14.131)	109.081 (± 14.524)	94.841 (± 14.434)	

Statistical analyses

Statistical analysis title	Disease Activity - 500 mg Avoralstat
Comparison groups	Avoralstat 500mg v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.589 [5]
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-10.903
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.789
upper limit	28.983

Notes:

[5] - ANCOVA Model includes terms of treatment and the randomization strata

Statistical analysis title	Disease Activity - 300 mg Avoralstat
Comparison groups	Avoralstat 300mg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.487 [6]
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	14.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.189
upper limit	54.669

Notes:

[6] - ANCOVA Model includes terms of treatment and the randomization strata

Secondary: Angioedema Quality of Life (AE-QoL)

End point title	Angioedema Quality of Life (AE-QoL)

End point description:

Quality of Life (QoL) specific to hereditary angioedema (HAE) was assessed via AE-QoL, which consists of 17 questions that spanned 4 domains (functioning, fatigue/mood, fear/shame, and nutrition). Each AE-QoL question had 5 answer options (scored 1-5), with lower and higher scores indicting less and more adverse impact, respectively. Per-subject scores for each domain were computed using the appropriate scoring algorithm applied to the question response scores for each domain. Per-subject total scores (including all 4 domains) were similarly computed using the question response scores for all 17 questions. The outputs from the scoring algorithm were normalized on a scale ranging from 0 (less adverse impact) to 100 (most adverse impact). The statistical analysis of the AE-QoL total score change from baseline to Week 12 is presented below.

End point type	Secondary

End point timeframe:

Angioedema Quality of Life questionnaire (AE QoL) was completed during clinic visits, prior to dosing on Day 1, and on Days 29, 57 & 85 (Weeks 4, 8 & 12) during the treatment period.

End point values	Avoralstat 500mg	Avoralstat 300mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	36	
Units: AE-QoL Score				
least squares mean (standard error)	-17.45 (± 2.66)	-9.89 (± 3.11)	-12.14 (± 2.64)	

Statistical analyses

Statistical analysis title	AE-QoL - 500 mg Avoralstat
Comparison groups	Avoralstat 500mg v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.162 [7]
Method	Mixed Model for Repeated Measures
Parameter estimate	Difference Least Mean Square
Point estimate	-5.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.8
upper limit	2.2

Notes:

[7] - Mixed model for repeated measures includes terms for baseline value, visit, treatment and visit by treatment interaction.

Statistical analysis title	AE-QoL - 300 mg Avoralstat
Comparison groups	Avoralstat 300mg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.585 [8]
Method	Mixed Model for Repeated Measures
Parameter estimate	Difference Least Mean Square
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	10.4

Notes:

[8] - Mixed model for repeated measures includes terms for baseline value, visit, treatment and visit by treatment interaction.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events (AEs) reported from informed consent signature until the follow-up visit (week 14) or until the AE is resolved or the subject is in a clinically stable condition with regards to the AE.	
Adverse event reporting additional description:	
Symptoms of HAE were not considered an AE unless they qualify as an SAE.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Avoralstat 500mg
Reporting group description:	
5x 100 mg Avoralstat capsules TID	
Reporting group title	Avoralstat 300mg
Reporting group description:	
3x 100 mg Avoralstat capsules + 2 matched placebo capsules TID	
Reporting group title	Placebo
Reporting group description:	
5x Placebo capsules TID	

Serious adverse events	Avoralstat 500mg	Avoralstat 300mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	2 / 36 (5.56%)	3 / 36 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
HAE			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
abortion, induced			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			

subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 36 (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
General disorders and administration site conditions			
chest discomfort			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 36 (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
Chest pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 36 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Avoralstat 500mg	Avoralstat 300mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	31 / 36 (86.11%)	32 / 36 (88.89%)
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 36 (8.33%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Blood urine present			
subjects affected / exposed	0 / 38 (0.00%)	3 / 36 (8.33%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 36 (8.33%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	7 / 38 (18.42%)	4 / 36 (11.11%)	6 / 36 (16.67%)
occurrences (all)	7	4	6
Somnolence			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 38 (5.26%)	3 / 36 (8.33%)	2 / 36 (5.56%)
occurrences (all)	2	3	2
Abdominal pain			
subjects affected / exposed	4 / 38 (10.53%)	0 / 36 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 38 (0.00%)	3 / 36 (8.33%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Dyspepsia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Faeces soft			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	3 / 36 (8.33%)
occurrences (all)	1	1	3
Flatulence			
subjects affected / exposed	10 / 38 (26.32%)	5 / 36 (13.89%)	9 / 36 (25.00%)
occurrences (all)	10	5	9
Nausea			
subjects affected / exposed	3 / 38 (7.89%)	4 / 36 (11.11%)	3 / 36 (8.33%)
occurrences (all)	3	4	3
Diarrhoea			

subjects affected / exposed	16 / 38 (42.11%)	8 / 36 (22.22%)	12 / 36 (33.33%)
occurrences (all)	16	8	12
Frequent bowel movements			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	3 / 36 (8.33%)
occurrences (all)	1	0	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Back pain			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Myalgia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			

Cystitis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Gastroenteritis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Influenza			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	8 / 38 (21.05%)	5 / 36 (13.89%)	7 / 36 (19.44%)
occurrences (all)	8	5	7
Oral herpes			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Sinusitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	3 / 36 (8.33%)
occurrences (all)	1	1	3
Tonsillitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	1 / 36 (2.78%)
occurrences (all)	2	1	1
Viral infection			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Pharyngitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences (all)	2	2	1

Tooth infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 36 (2.78%) 1	2 / 36 (5.56%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2014	UK-Specific Amendment: - Inclusion criterion 4a was modified to indicate that 2 highly effective contraceptive methods must be used by females of childbearing potential. Two or more of the following methods were identified as acceptable and had to include at least one barrier method: surgical sterilization (i.e. bilateral tubal ligation); placement of an intrauterine device or intrauterine system; hormonal contraception (implantable, patch, oral, vaginal ring); or barrier methods (either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm, or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository). Estrogen- and progestin-containing hormonal contraception was only permitted if it had been initiated within 60 days prior to screening or expected to be initiated at any time through the end of the study (follow-up); IUDs with progestin were permitted to be placed at any time prior to or during screening. - Inclusion criteria 4c (females) and 5a (males) was modified to include a clear definition of abstinence as true abstinence when in line with the preferred and usual lifestyle of the subject. - Inclusion criterion 5a was modified to indicate that male participants were required to utilize a highly effective contraceptive method with female partners of childbearing potential (defined as postmenopausal ≤ 2 years or a non-menopausal female who had not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure). The term "highly effective contraceptive method" was defined as having had a vasectomy, or utilizing 2 forms of contraception, 1 of which must have been a condom, during intercourse, for the study duration and for 90 days after the last dose of the study drug.
15 April 2015	Canada-specific Amendment: Canada was added to the list of countries in which study centers were located.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported