Clinical trial results:
A Double-blind, Placebo-controlled, Randomized Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in the Treatment of Idiopathic Hypersomnia (IH) with an Open-label Safety Extension

Summary

EudraCT number	2018-001311-79
Trial protocol	FR GB CZ BE DE ES FI IT
Global end of trial date	18 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	JZP080-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03533114
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 49,641

Notes:

Sponsors

Sponsor organisation name	Jazz Pharmaceuticals Inc.
Sponsor organisation address	3170 Porter Drive, Palo Alto, United States, 94304
Public contact	Director, Jazz Pharmaceuticals, +1 2158323750 , ClinicalTrialDisclosure@JazzPharma.com
Scientific contact	Director, Jazz Pharmaceuticals, +1 2158323750 , ClinicalTrialDisclosure@JazzPharma.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	30 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2020
Global end of trial reached?	Yes
Global end of trial date	18 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of JZP-258 in the treatment of IH.

Protection of trial subjects:

A written informed consent form (ICF) was obtained before any study procedure were performed in the study and the date of the written consent was obtained and documented.

Participants who participated in the pharmacokinetic (PK) assessments signed a separate ICF prior to any PK assessments being performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2018
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	Poland: 4
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	United States: 104
Worldwide total number of subjects	154
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)	144
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The safety population is categorized according to the presence or absence of medications used to treat IH symptoms at the time of study baseline.

Pre-assignment

Screening details:

The screening period was 14 to 30 days, with the option to rescreen once.

Period 1

Period 1 title	Open Label Titration and Optimization
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Baseline evaluations were done prior to first dose. Study drug administration began on day 1. Participants were titrated to their optimal dose.

Arms

Are arms mutually exclusive?	Yes
Arm title	On Baseline IH Medication

Arm description:

Participants treated with medication for IH at baseline.

Arm type	Experimental
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were begun on JZP-258 either as a once nightly or twice nightly dosing regimen at the discretion of the investigator. The dosing regimen of JZP-258 could then be adjusted until an optimally effective and tolerable dosing regimen was established. Participants on Xyrem at baseline were switched to the same dose of JZP-258. The dosing regimen could then be adjusted until an optimally effective and tolerable dosing regimen was established (if needed.)

Arm title	Treatment Naive

Arm description:

Participants not treated with medication for IH at baseline.

Arm type	Experimental
Investigational medicinal product name	JZP258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were begun on JZP-258 either as a once nightly or twice nightly dosing regimen at the discretion of the investigator. The dosing regimen of JZP-258 could then be adjusted until an optimally effective and tolerable dosing regimen was established.

Number of subjects in period 1	On Baseline IH Medication	Treatment Naive
Started	88	66
Completed	72	53
Not completed	16	13
Consent withdrawn by subject	2	-
Non-Compliance with Study Drug	-	1
Adverse event, non-fatal	11	8
Lost to follow-up	-	1
Lack of efficacy	3	1
Withdrawal by subject	-	1
Protocol deviation	-	1

Period 2	
Period 2 title	Stable Dose
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	No
Arm title	On Baseline IH Medication
Arm description: Participants treated with medication for IH at baseline.	
Arm type	Experimental
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details: Participants continued on their optimized stable dose.	
Arm title	Treatment Naive
Arm description: Participants not treated with medication for IH at baseline.	
Arm type	Experimental

Investigational medicinal product name	JZP258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants continued on their optimized stable dose.

Number of subjects in period 2	On Baseline IH Medication	Treatment Naive
Started	71	52
Completed	69	50
Not completed	2	2
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	2
Lack of efficacy	1	-

Period 3

Period 3 title	Double Blind Randomized-Withdrawal
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	On Baseline IH Medication

Arm description:

Participants treated with medication for IH at baseline.

Arm type	Experimental versus Placebo
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were randomized 1:1 to continue their same dose of JZP-258 or placebo.

Arm title	Treatment Naive

Arm description:

Participants not treated with medication for IH at baseline.

Arm type	Experimental versus Placebo

Investigational medicinal product name	JZP258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were randomized 1:1 to continue their same dose of JZP-258 or placebo.

Number of subjects in period 3	On Baseline IH Medication	Treatment Naive
Started	69	47
Completed	67	46
Not completed	2	1
Failure to meet randomization criteria	1	-
Adverse event, non-fatal	1	1

Period 4

Period 4 title	Open-Label Safety Extension
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	On Baseline IH Medication

Arm description:

Participants treated with medication for IH at baseline.

Arm type	Experimental
Investigational medicinal product name	JZP-258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

All participants were treated with JZP-258.

Arm title	Treatment Naive

Arm description:

Participants not treated with medication for IH at baseline.

Arm type	Experimental

Investigational medicinal product name	JZP258
Investigational medicinal product code	
Other name	mixed oxybate salts; calcium, magnesium, potassium, sodium oxybate; Xywav
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

All participants were treated with JZP-258

Number of subjects in period 4[1]	On Baseline IH Medication	Treatment Naive
Started	65	41
Completed	57	38
Not completed	8	3
Consent withdrawn by subject	2	3
Adverse event, non-fatal	3	-
Lost to follow-up	1	-
Lack of efficacy	1	-
Protocol deviation	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: To best evaluate safety with the DBRW design, we use the safety observations from all of the time frames in which patients were treated with JZP-258. These time frames are: the Open-label Treatment Titration and Optimization Period, the Stable Dose Period, the Double-blind Randomized Withdrawal Period, and the Open-label Safety Extension Period. Safety was evaluated in two groups ("Receiving Baseline IH Medication", and "Naïve").

Baseline characteristics

Reporting groups	
Reporting group title	On Baseline IH Medication
Reporting group description:	
Participants treated with medication for IH at baseline.	
Reporting group title	Treatment Naive
Reporting group description:	
Participants not treated with medication for IH at baseline.	

Reporting group values	On Baseline IH Medication	Treatment Naive	Total
Number of subjects	88	66	154
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	41.0	39.4	
standard deviation	± 13.37	± 14.25	-
Gender categorical Units: Subjects			
Female	65	40	105
Male	23	26	49

Subject analysis sets	
Subject analysis set title	JZP-258
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent to Treat (mITT) analysis set included all participants who were randomized to JZP258 or placebo, who received at least 1 dose of study drug during the DBRW and have had at least one set of post randomization assessments for ESS or IHSS, or a PGIc value at the end of the DBRW.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent to Treat (mITT) analysis set included all participants who were randomized to JZP258 or placebo, who received at least 1 dose of study drug during the DBRW and have had at least one set of post randomization assessments for ESS or IHSS, or a PGIc value at the end of the DBRW.	

Reporting group values	JZP-258	Placebo	
Number of subjects	56	59	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	43.4	38.5	
standard deviation	± 14.44	± 13.01	
Gender categorical Units: Subjects			
Female	39	43	
Male	17	16	

End points

End points reporting groups

Reporting group title	On Baseline IH Medication
Reporting group description:	
Participants treated with medication for IH at baseline.	
Reporting group title	Treatment Naive
Reporting group description:	
Participants not treated with medication for IH at baseline.	
Reporting group title	On Baseline IH Medication
Reporting group description:	
Participants treated with medication for IH at baseline.	
Reporting group title	Treatment Naive
Reporting group description:	
Participants not treated with medication for IH at baseline.	
Reporting group title	On Baseline IH Medication
Reporting group description:	
Participants treated with medication for IH at baseline.	
Reporting group title	Treatment Naive
Reporting group description:	
Participants not treated with medication for IH at baseline.	
Reporting group title	On Baseline IH Medication
Reporting group description:	
Participants treated with medication for IH at baseline.	
Reporting group title	Treatment Naive
Reporting group description:	
Participants not treated with medication for IH at baseline.	
Subject analysis set title	JZP-258
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent to Treat (mITT) analysis set included all participants who were randomized to JZP258 or placebo, who received at least 1 dose of study drug during the DBRW and have had at least one set of post randomization assessments for ESS or IHSS, or a PGIc value at the end of the DBRW.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent to Treat (mITT) analysis set included all participants who were randomized to JZP258 or placebo, who received at least 1 dose of study drug during the DBRW and have had at least one set of post randomization assessments for ESS or IHSS, or a PGIc value at the end of the DBRW.	

Primary: Change in Epworth Sleepiness Scale (ESS) score

End point title	Change in Epworth Sleepiness Scale (ESS) score
End point description:	
The ESS is a 8-item self reported questionnaire intended to measure daytime sleepiness. In this test, participants answer questions with regard to the level of sleepiness they experienced over approximately the 7 days prior to the assessment while performing eight common, non-stimulating activities. The ESS total score range is 1 to 24. Each activity is rated on a 4-point scale ranging from a minimum of "would never doze" to a maximum of "a high chance of dozing." Thus, the ESS scale range is as follows: 0=would never doze, 1=slight chance of dozing, 2=moderate chance of dozing, 3=high chance of dozing; 0 indicates a better outcome, and 3 indicates a worse outcome. A positive mean change value indicates an increase in score from the end of the stable dose period and worsened daytime sleepiness. A higher ESS score (above 10) reflects a greater average sleep propensity in daily life (ASP) , or daytime sleepiness.	
End point type	Primary

End point timeframe:

Change from the end of the Stable Dose Period to the end of the Double-blind Randomized Withdrawal Period (DBRW) (2 Weeks)

End point values	JZP-258	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	59		
Units: score on a scale				
arithmetic mean (standard deviation)	0.7 (± 3.22)	7.4 (± 5.16)		

Statistical analyses

Statistical analysis title	Change from Baseline in ESS Score
Comparison groups	JZP-258 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.99
upper limit	-5.03

Notes:

[1] - Mixed model analysis of covariance to compare treatment groups, with the change in ESS total score from the end of the SDP to the end of DBRWP as the response variable, with fixed effects of treatment group and baseline medication group and covariate of ESS total score at the end of the SDP.

Secondary: Percentage of Participants Reported as Worse on the Patient Global Impression of Change (PGIc)

End point title	Percentage of Participants Reported as Worse on the Patient Global Impression of Change (PGIc)

End point description:

The Patient Global Impression - Change (PGIc) scale was completed by the participant. The PGI-C scale rated the participant's condition at a specified time point on a 7-point scale ranging from a minimum of "Very much improved" to a maximum of "Very much worse." The PGIc scale consists of the following ratings: 1-Very Much improved, 2-Much improved, 3-Minimally improved, 4-No change, 5-Minimally worse, 6-Much worse, 7-Very much worse; a rating of 1 indicates a better outcome, and a rating of 7 indicates a worse outcome. Worsened condition was defined as a PGIc rating of 5, 6, or 7.

End point type	Secondary

End point timeframe:

At the end of the DBRW Period (2 Weeks)

End point values	JZP-258	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	59		
Units: percentage of participants	12	52		

Statistical analyses

Statistical analysis title	Participants who worsen in PGIc in DBWP
Comparison groups	JZP-258 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in Proportion
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.53

Notes:

[2] - Cochran-Mantel-Haenszel test, stratified by baseline medication group, to compare the difference between treatment groups in the proportion of participants who worsen (very much worse, much worse, minimally worse) in the PGIc assessment at the end of DBRWP.

Secondary: Change in Total Score on the Idiopathic Hypersomnia Severity Scale (IHSS)

End point title	Change in Total Score on the Idiopathic Hypersomnia Severity Scale (IHSS)

End point description:

The IHSS is a 14-item self-reported questionnaire assessing the severity of IH symptoms of excessive sleepiness, prolonged sleep duration, cognitive impairment and sleep inertia. Total scores can range from 0 to 50, with higher scores indicating a greater severity or frequency of symptoms.

End point type	Secondary

End point timeframe:

Change from the end of the Stable Dose Period to the end of the DBRW Period (2 Weeks)

End point values	JZP-258	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	59		
Units: score on a scale				
median (full range (min-max))	0.0 (-8 to 24)	14.0 (-2 to 38)		

Statistical analyses

Statistical analysis title	Change from Baseline in IHSS score
Comparison groups	Placebo v JZP-258
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	-8

Notes:

[3] - The estimated median difference between treatment groups are obtained from a Hodges-Lehmann estimate. The p-value is obtained from a rank based, mixed-model analysis of covariance to compare treatment groups, with the change in IHSS total score from the end of the SDP to the end of DBRWP as the response variable, with fixed effects of treatment group and baseline medication group and covariate of ranked IHSS total score at the end of the SDP.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) and Serious Adverse Events (SAEs) were recorded from the time on or after the first dose of study drug, including adverse events that occurred until 30 days after the last dose date up to 42 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	On Baseline IH Medication
Reporting group description:	
Participants treated with medication for IH at baseline.	
Reporting group title	Treatment Naive
Reporting group description:	
Participants not treated with medication for IH at baseline.	

Serious adverse events	On Baseline IH Medication	Treatment Naive	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 88 (2.27%)	2 / 66 (3.03%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 88 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 88 (1.14%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	On Baseline IH Medication	Treatment Naive	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 88 (72.73%)	39 / 66 (59.09%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 88 (5.68%)	1 / 66 (1.52%)	
occurrences (all)	5	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 88 (9.09%)	11 / 66 (16.67%)	
occurrences (all)	8	11	
Headache			
subjects affected / exposed	15 / 88 (17.05%)	12 / 66 (18.18%)	
occurrences (all)	26	16	
Paraesthesia			
subjects affected / exposed	5 / 88 (5.68%)	0 / 66 (0.00%)	
occurrences (all)	5	0	
Somnolence			
subjects affected / exposed	5 / 88 (5.68%)	4 / 66 (6.06%)	
occurrences (all)	6	5	
Tremor			

subjects affected / exposed	9 / 88 (10.23%)	0 / 66 (0.00%)	
occurrences (all)	11	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 88 (9.09%)	4 / 66 (6.06%)	
occurrences (all)	10	5	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 88 (5.68%)	1 / 66 (1.52%)	
occurrences (all)	5	1	
Diarrhoea			
subjects affected / exposed	11 / 88 (12.50%)	3 / 66 (4.55%)	
occurrences (all)	15	4	
Dry mouth			
subjects affected / exposed	8 / 88 (9.09%)	2 / 66 (3.03%)	
occurrences (all)	8	2	
Nausea			
subjects affected / exposed	21 / 88 (23.86%)	13 / 66 (19.70%)	
occurrences (all)	31	14	
Vomiting			
subjects affected / exposed	15 / 88 (17.05%)	3 / 66 (4.55%)	
occurrences (all)	18	3	
Respiratory, thoracic and mediastinal disorders			
Snoring			
subjects affected / exposed	1 / 88 (1.14%)	4 / 66 (6.06%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	7 / 88 (7.95%)	2 / 66 (3.03%)	
occurrences (all)	10	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 88 (11.36%)	8 / 66 (12.12%)	
occurrences (all)	11	8	
Insomnia			

subjects affected / exposed	13 / 88 (14.77%)	4 / 66 (6.06%)	
occurrences (all)	15	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 88 (5.68%)	2 / 66 (3.03%)	
occurrences (all)	6	3	
Muscle spasms			
subjects affected / exposed	7 / 88 (7.95%)	1 / 66 (1.52%)	
occurrences (all)	9	1	
Pain in extremity			
subjects affected / exposed	6 / 88 (6.82%)	0 / 66 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 88 (6.82%)	6 / 66 (9.09%)	
occurrences (all)	6	7	
Sinusitis			
subjects affected / exposed	1 / 88 (1.14%)	4 / 66 (6.06%)	
occurrences (all)	1	5	
Upper respiratory tract infection			
subjects affected / exposed	7 / 88 (7.95%)	5 / 66 (7.58%)	
occurrences (all)	7	6	
Urinary tract infection			
subjects affected / exposed	6 / 88 (6.82%)	6 / 66 (9.09%)	
occurrences (all)	7	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 88 (7.95%)	7 / 66 (10.61%)	
occurrences (all)	7	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported