



Clinical trial results:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Effect of VX-770 on Lung Clearance Index in Subjects with Cystic Fibrosis, the G551D Mutation, and FEV1 >90% Predicted

Summary

EudraCT number	2010-020546-96
Trial protocol	GB
Global end of trial date	30 November 2011

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	VX10-770-106
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01262352
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 022101862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000335-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of VX-770 on lung clearance index (LCI) in subjects aged 6 years and older with cystic fibrosis (CF) who have the G551D CFTR mutation on at least 1 allele.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2011
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: 9
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	20
EEA total number of subjects	9

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)	8
Adolescents (12-17 years)	8
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started on 14 February 2011 (signing of first informed consent). After obtaining informed consent and assent (where applicable), screening evaluations were completed at any time during the period 10 to 18 days (Days -18 to -10) before first dose of study drug (Day 1).

Pre-assignment

Screening details:

A total of 21 subjects were randomized; 20 subjects received at least 1 dose of the study drug.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Sequence 1: Ivacaftor Then Placebo

Arm description:

Ivacaftor administered in Treatment Period 1 and placebo administered in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor every 12 hours (q12h) for up to 28 days.

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

Dosage and administration details:

Oral tablet q12h for up to 28 days.

Arm title	Sequence 2: Placebo Then Ivacaftor
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Arm description:

Placebo administered in Treatment Period 1 and ivacaftor administered in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor q12h for up to 28 days.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Oral tablet q12h for up to 28 days.	

Number of subjects in period 1	Sequence 1: Ivacaftor Then Placebo	Sequence 2: Placebo Then Ivacaftor
Started	10	10
Completed	10	10

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	Sequence 1: Ivacaftor Then Placebo

Arm description:

Ivacaftor administered in Treatment Period 1 and placebo administered in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor q12h for up to 28 days.

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

Dosage and administration details:

Oral tablet q12h for up to 28 days.

Arm title	Sequence 2: Placebo Then Ivacaftor
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Arm description:

Placebo administered in treatment period 1 and ivacaftor administered in treatment period 2.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor q12h for up to 28 days.

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

Dosage and administration details:

Oral tablet q12h for up to 28 days.

Number of subjects in period 2	Sequence 1: Ivacaftor Then Placebo	Sequence 2: Placebo Then Ivacaftor
Started	9	8
Completed	9	8

Baseline characteristics

Reporting groups

Reporting group title	Sequence 1: Ivacaftor Then Placebo
Reporting group description: Ivacaftor administered in Treatment Period 1 and placebo administered in Treatment Period 2.	
Reporting group title	Sequence 2: Placebo Then Ivacaftor
Reporting group description: Placebo administered in Treatment Period 1 and ivacaftor administered in Treatment Period 2.	

Reporting group values	Sequence 1: Ivacaftor Then Placebo	Sequence 2: Placebo Then Ivacaftor	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
<=18 years	9	7	16
Between 18 and 65 years	1	3	4
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	13.4	19.8	
standard deviation	± 7.12	± 13.35	-
Gender categorical Units: Subjects			
Female	6	4	10
Male	4	6	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	10	10	20
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	10	20
More than one race	0	0	0
Region of Enrollment Units: Subjects			
North America	6	5	11
Europe	4	5	9
Height Units: centimeters			
arithmetic mean	148.9	156	
standard deviation	± 19.54	± 17.92	-
Weight			

Units: kilograms arithmetic mean standard deviation	45.06 ± 20.018	58.78 ± 30.576	-
Body Mass Index Units: kilograms per square meter arithmetic mean standard deviation	19.36 ± 3.707	22.66 ± 6.964	-
Lung Clearance Index (LCI) Units: ratio arithmetic mean standard deviation	9.17 ± 1.657	8.88 ± 1.462	-
Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Units: percentage arithmetic mean standard deviation	101.83 ± 11.587	92.58 ± 7.427	-
Sweat Chloride Units: millimoles per liter arithmetic mean standard deviation	97.1 ± 7.4	86.17 ± 19.219	-

End points

End points reporting groups

Reporting group title	Sequence 1: Ivacaftor Then Placebo
Reporting group description: Ivacaftor administered in Treatment Period 1 and placebo administered in Treatment Period 2.	
Reporting group title	Sequence 2: Placebo Then Ivacaftor
Reporting group description: Placebo administered in Treatment Period 1 and ivacaftor administered in Treatment Period 2.	
Reporting group title	Sequence 1: Ivacaftor Then Placebo
Reporting group description: Ivacaftor administered in Treatment Period 1 and placebo administered in Treatment Period 2.	
Reporting group title	Sequence 2: Placebo Then Ivacaftor
Reporting group description: Placebo administered in treatment period 1 and ivacaftor administered in treatment period 2.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Oral tablet every 12 hours (q12h) for up to 28 days.	
Subject analysis set title	Ivacaftor
Subject analysis set type	Full analysis
Subject analysis set description: Oral tablet of 150 mg of ivacaftor q12h for up to 28 days.	

Primary: Absolute Change From Baseline in Lung Clearance Index (LCI) Through Day 29

End point title	Absolute Change From Baseline in Lung Clearance Index (LCI) Through Day 29 ^[1]
End point description: Lung clearance index (LCI) is a measure of ventilation inhomogeneity that is derived from a multiple-breath washout test. The LCI was calculated as the number of lung volume turnovers (cumulative expired volume divided by the functional residual capacity [FRC]) required to reduce end-tidal SF6 concentration to 1/40th of the starting value. Analysis was performed for all randomized subjects who received at least 1 dose of study drug (placebo or ivacaftor) and had available assessments during the time frame.	
End point type	Primary
End point timeframe: Baseline through Day 29	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical Analysis is provided in the attachment.

End point values	Placebo	Ivacaftor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	17		
Units: ratio				
least squares mean (standard error)	0.77 (± 0.291)	-1.3 (± 0.303)		

Attachments (see zip file)	Statistical Analysis/Absolute Change From Baseline in LCI
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Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in ppFEV1 Through Day 29

End point title	Absolute Change From Baseline in ppFEV1 Through Day 29
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End point description:

Spirometry (as measured by ppFEV1) is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies. Analysis was performed for all randomized subjects who received at least 1 dose of study drug (placebo or ivacaftor) and had available assessments during the time frame.

End point type	Secondary
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End point timeframe:

Baseline through Day 29

End point values	Placebo	Ivacaftor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: percent				
least squares mean (standard error)	0 ($\pm$ 1.916)	7 ($\pm$ 1.978)		

Attachments (see zip file)	Statistical Analysis/Absolute Change From Baseline in ppFEV1
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sweat Chloride Through Day 29

End point title	Change From Baseline in Sweat Chloride Through Day 29
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End point description:

The sweat chloride (quantitative pilocarpine iontophoresis) test is a standard diagnostic tool for cystic fibrosis (CF), serving as an indicator of cystic fibrosis transmembrane conductance regulator (CFTR) activity. Analysis was performed for all randomized subjects who received at least 1 dose of study drug (placebo or ivacaftor) and had available assessments during the time frame.

End point type	Secondary
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End point timeframe:

Baseline through Day 29

End point values	Placebo	Ivacaftor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	16		
Units: millimoles per liter				
least squares mean (standard error)	0.11 ($\pm$ 2.351)	-45.74 ($\pm$ 2.632)		

Attachments (see zip file)	Statistical Analysis/Change From Baseline in Sweat Chloride
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CF Questionnaire-Revised (CFQ-R) Score (Respiratory Domain Score, Pooled) Through Day 29

End point title	Change From Baseline in CF Questionnaire-Revised (CFQ-R) Score (Respiratory Domain Score, Pooled) Through Day 29
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End point description:

The CFQ-R is a health-related quality of life measure for subjects with cystic fibrosis. Each domain is scored from 0 (worst) to 100 (best). A difference of at least 4 points in the respiratory domain score of the CFQ-R is considered a minimal clinically important difference (MCID). Analysis was performed for all randomized subjects who received at least 1 dose of study drug (placebo or ivacaftor) and had available assessments during the time frame.

End point type	Secondary
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End point timeframe:

Baseline through Day 29

End point values	Placebo	Ivacaftor		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: score on a scale				
least squares mean (standard error)	1.33 ($\pm$ 3.067)	5.32 ($\pm$ 3.166)		

Attachments (see zip file)	Statistical Analysis/Change From Baseline in CFQ-R Score
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For enrolled subjects, all adverse events were collected through the Follow-up Visit (4 weeks [+/-7 days] after the last dose of study drug).

Adverse event reporting additional description:

For subjects who were screened but were not subsequently enrolled in the study, all adverse events were collected until the subject was deemed ineligible for the study. Treatment-emergent adverse events are reported here.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Oral tablet every 12 hours (q12h) for up to 28 days.

Reporting group title	Ivacaftor
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Reporting group description:

Oral tablet of 150 mg of ivacaftor q12h for up to 28 days.

Serious adverse events	Placebo	Ivacaftor	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	2 / 18 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal ileal Obstruction syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis allergic			

subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
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: 0 %

Non-serious adverse events	Placebo	Ivacaftor	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)	13 / 18 (72.22%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 19 (15.79%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Fatigue			
subjects affected / exposed	1 / 19 (5.26%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Application site papules			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 19 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Nipple disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nipple pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Cough		
subjects affected / exposed	7 / 19 (36.84%)	5 / 18 (27.78%)
occurrences (all)	10	5
Nasal congestion		
subjects affected / exposed	2 / 19 (10.53%)	1 / 18 (5.56%)
occurrences (all)	2	1
Oropharyngeal pain		
subjects affected / exposed	2 / 19 (10.53%)	0 / 18 (0.00%)
occurrences (all)	2	0
Productive cough		
subjects affected / exposed	1 / 19 (5.26%)	1 / 18 (5.56%)
occurrences (all)	1	1
Epistaxis		
subjects affected / exposed	1 / 19 (5.26%)	1 / 18 (5.56%)
occurrences (all)	1	1
Nasal inflammation		
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	1	0
Nasal oedema		
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	1	0
Rales		
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	1
Respiratory tract congestion		
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	1	0
Rhinorrhoea		
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	1	0
Sinus congestion		
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	2	0
Sneezing		
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)
occurrences (all)	1	0

Investigations			
Bacteria sputum identified			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Bacterial culture positive			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Lymph node palpable			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Prothrombin time prolonged			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Bite			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Joint sprain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Medical device complication			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 19 (5.26%)	4 / 18 (22.22%)	
occurrences (all)	1	4	
Dizziness			

subjects affected / exposed	0 / 19 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	3	
Hypoaesthesia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 19 (21.05%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Abdominal pain upper			
subjects affected / exposed	2 / 19 (10.53%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	1 / 19 (5.26%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Abdominal tenderness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hiatus hernia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Rash macular subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 18 (5.56%) 1	
Acne subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Blister subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Swelling face subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Renal and urinary disorders Glycosuria subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Haematuria subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Back pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Myalgia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Infections and infestations			

Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	0 / 18 (0.00%) 0	
Gastrointestinal viral infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Mycobacterium abscessus infection subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 18 (5.56%) 1	
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Pneumococcal infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Staphylococcal infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	
Metabolism and nutrition disorders Glucose tolerance impaired subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 18 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2010	LCI assessments were updated; hypertonic saline restrictions were changed; discontinuation criteria related to liver tests and criteria for replacing subjects were updated.
29 July 2010	LCI measurements technique was clarified; minimum number of enrolled subjects was updated.
07 January 2011	ECG assessments were updated; interim analysis of the data was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Statistical analysis is provided in attachment for individual endpoint.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24461666>