Clinical trial results:
A Phase 3, Two-Part, Randomized, Double-Blind, Placebo-Controlled, Crossover Study With an Open-Label Period to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D CFTR Gating Mutation

Summary

EudraCT number	2012-000388-26
Trial protocol	BE
Global end of trial date	14 October 2013

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	VX12-770-111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01614470
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 877634 8789, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 877634 8789, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	02 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ivacaftor in subjects with cystic fibrosis (CF) who have a non-G551D CF transmembrane conductance regulator (CFTR) gating mutation.

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	11 July 2012
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	France: 8
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	39
EEA total number of subjects	17

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)	11
Adults (18-64 years)	20

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a Screening Period (Day -35 to Day -15 relative to the first dose of study drug). A total of 42 subjects were screened, of which 39 subjects were randomized.

Period 1

Period 1 title	Part 1: Treatment Period 1 (8 Weeks)
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?	Yes
Arm title	Sequence 1: Ivacaftor First, Then Placebo

Arm description:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 8 weeks in treatment period 1 followed by placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.

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

Dosage and administration details:

Ivacaftor 150 mg tablet orally twice daily for 8 weeks.

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

Dosage and administration details:

Placebo matched to ivacaftor tablet orally twice daily for 8 weeks.

Arm title	Sequence 2: Placebo First, Then Ivacaftor

Arm description:

Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 1 followed by ivacaftor 150 mg tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.

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

Dosage and administration details:

Placebo matched to ivacaftor tablet orally twice daily for 8 weeks.

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

Dosage and administration details:

Ivacaftor 150 mg tablet orally twice daily for 8 weeks.

Number of subjects in period 1	Sequence 1: Ivacaftor First, Then Placebo	Sequence 2: Placebo First, Then Ivacaftor
Started	20	19
Completed	18	18
Not completed	2	1
Need to extend washout period	1	1
Lost to follow-up	1	-

Period 2

Period 2 title	Part 1: Treatment Period 2 (8 Weeks)
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?	Yes
Arm title	Sequence 1: Ivacaftor First, Then Placebo

Arm description:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 8 weeks in treatment period 1 followed by placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.

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

Dosage and administration details:

Ivacaftor 150 mg tablet orally twice daily for 8 weeks.

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

Dosage and administration details:

Placebo matched to ivacaftor tablet orally twice daily for 8 weeks.

Arm title	Sequence 2: Placebo First, Then Ivacaftor

Arm description:

Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 1 followed by ivacaftor 150 mg tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.

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

Dosage and administration details:

Placebo matched to ivacaftor tablet orally twice daily for 8 weeks.

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

Dosage and administration details:

Ivacaftor 150 mg tablet orally twice daily for 8 weeks.

Number of subjects in period 2	Sequence 1: Ivacaftor First, Then Placebo	Sequence 2: Placebo First, Then Ivacaftor
Started	18	18
Completed	18	18

Period 3

Period 3 title	Part 2: Open-label Extension (16 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label Extension (OLE) Ivacaftor

Arm description:

Ivacaftor 150 mg tablet orally twice daily for 16 weeks.

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

Dosage and administration details:

Ivacaftor 150 mg tablet orally twice daily for 16 weeks.

Number of subjects in period 3	Open-label Extension (OLE) Ivacaftor
Started	36
Completed	36

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1: Ivacaftor First, Then Placebo
Reporting group description:	
Ivacaftor 150 milligram (mg) tablet orally twice daily for 8 weeks in treatment period 1 followed by placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.	
Reporting group title	Sequence 2: Placebo First, Then Ivacaftor
Reporting group description:	
Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 1 followed by ivacaftor 150 mg tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.	

Reporting group values	Sequence 1: Ivacaftor First, Then Placebo	Sequence 2: Placebo First, Then Ivacaftor	Total
Number of subjects	20	19	39
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	23.8	21.7	
standard deviation	± 13.25	± 12.92	-
Gender categorical			
Units: Subjects			
Female	7	10	17
Male	13	9	22

End points

End points reporting groups

Reporting group title	Sequence 1: Ivacaftor First, Then Placebo
Reporting group description:	
Ivacaftor 150 milligram (mg) tablet orally twice daily for 8 weeks in treatment period 1 followed by placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.	
Reporting group title	Sequence 2: Placebo First, Then Ivacaftor
Reporting group description:	
Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 1 followed by ivacaftor 150 mg tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.	
Reporting group title	Sequence 1: Ivacaftor First, Then Placebo
Reporting group description:	
Ivacaftor 150 milligram (mg) tablet orally twice daily for 8 weeks in treatment period 1 followed by placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.	
Reporting group title	Sequence 2: Placebo First, Then Ivacaftor
Reporting group description:	
Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in treatment period 1 followed by ivacaftor 150 mg tablet orally twice daily for 8 weeks in treatment period 2. Washout out period of 4 to 8 weeks was maintained between each treatment period.	
Reporting group title	Open-label Extension (OLE) Ivacaftor
Reporting group description:	
Ivacaftor 150 mg tablet orally twice daily for 16 weeks.	
Subject analysis set title	Part 1 Treatment Period 2: Ivacaftor, Part 2: OLE Ivacaftor
Subject analysis set type	Full analysis
Subject analysis set description:	
Ivacaftor 150 mg tablet orally twice daily for 24 weeks (8 weeks in Part 1: Treatment Period 2 and 16 weeks in Part 2).	
Subject analysis set title	Part 1: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in any either Sequence 1 or Sequence 2.	
Subject analysis set title	Part 1: Ivacaftor
Subject analysis set type	Full analysis
Subject analysis set description:	
Ivacaftor 150 mg tablet orally twice daily for 8 weeks in either Sequence 1 or Sequence 2.	

Primary: Part 1: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 8

End point title	Part 1: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 8[1]
End point description:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Hankinson and Wang standards were used to calculate ppFEV1 (for age, gender, and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 6 to 17 years and for female subjects aged 6 to 15 years. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during study Part 1. Analysis was performed on Full Analysis Set (FAS) for Part 1 defined as all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).	
End point type	Primary

End point timeframe:

Part 1: Baseline through Week 8

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	Part 1: Ivacaftor	Part 1: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: percent predicted of FEV1				
least squares mean (standard error)	7.4868 (± 1.2292)	-3.1912 (± 1.2459)		

Attachments (see zip file)	Statistical Analysis/Part 1 - Absolute Change From Baseline in

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Absolute Change From Baseline in ppFEV1 at 24 Weeks of Treatment (Week 36 Visit)

End point title	Part 2: Absolute Change From Baseline in ppFEV1 at 24 Weeks of Treatment (Week 36 Visit)[2]

End point description:

FEV1 and ppFEV1 are defined in primary endpoint. Absolute change in ppFEV1 at 24 weeks of ivacaftor treatment (from Week 12 [Part 1: Treatment Period 2] at Week 36 [Part 2]) was reported for subjects who received ivacaftor in Part 1: Treatment Period 2, as per planned analysis. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during Part 1: Treatment Period 2. Analysis was performed on FAS for Part 2 defined as all randomized subjects who received at least 1 dose of study drug (ivacaftor).

End point type	Primary

End point timeframe:

Baseline (pre-dose Week 12), Week 36

Notes:

[2] - 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: No statistical analysis was planned for Part 2.

End point values	Part 1 Treatment Period 2: Ivacaftor, Part 2: OLE Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: percent predicted of FEV1				
arithmetic mean (standard deviation)				
Baseline	74.8375 (± 19.36754)			
Change at Week 36	13.5307 (± 10.18174)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Absolute Change From Baseline in Body Mass Index (BMI) Through Week 8

End point title	Part 1: Absolute Change From Baseline in Body Mass Index (BMI) Through Week 8

End point description:

BMI was defined as weight in kilogram (kg) divided by height in meters^2 (m^2). Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during study Part 1. Analysis was performed on FAS for Part 1.

End point type	Secondary

End point timeframe:

Part 1: Baseline through Week 8

End point values	Part 1: Ivacaftor	Part 1: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: kg/m^2				
least squares mean (standard error)	0.6787 (± 0.4948)	0.0163 (± 0.4954)		

Attachments (see zip file)	Statistical Analysis/Part 1 - Absolute Change From Baseline in

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absolute Change From Baseline in BMI at 24 Weeks of Treatment (Week 36 Visit)

End point title	Part 2: Absolute Change From Baseline in BMI at 24 Weeks of Treatment (Week 36 Visit)

End point description:

Absolute change in BMI at 24 weeks of ivacaftor treatment (from Week 12 [Part 1: Treatment Period 2] at Week 36 [Part 2]) was reported for subjects who received ivacaftor in Part 1: Treatment Period 2 as per planned analysis. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during Part 1: Treatment Period 2. Analysis was performed on FAS for Part 2.

End point type	Secondary

End point timeframe:

Baseline (pre-dose Week 12), Week 36

End point values	Part 1 Treatment Period 2: Ivacaftor, Part 2: OLE Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline	22.222 (± 6.2919)			
Change at Week 36	1.263 (± 0.7588)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Absolute Change From Baseline in Sweat Chloride Through Week 8

End point title	Part 1: Absolute Change From Baseline in Sweat Chloride Through Week 8

End point description:

Sweat samples were collected using an approved Macroduct (Wescor, Logan, Utah) collection device. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during study Part 1. Analysis was performed on FAS for Part 1.

End point type	Secondary

End point timeframe:

Part 1: Baseline through Week 8

End point values	Part 1: Ivacaftor	Part 1: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	37		
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	-52.2801 (± 2.721)	-3.1134 (± 2.7172)		

Attachments (see zip file)	Statistical Analysis/Part 1 - Absolute Change From Baseline in

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absolute Change From Baseline in Sweat Chloride at 24 Weeks of Treatment (Week 36 Visit)

End point title	Part 2: Absolute Change From Baseline in Sweat Chloride at 24 Weeks of Treatment (Week 36 Visit)

End point description:

Absolute change in sweat chloride at 24 weeks of ivacaftor treatment (from Week 12 [Part 1: Treatment Period 2] at Week 36 [Part 2]) was reported for subjects who received ivacaftor in Part 1: Treatment Period 2 as per planned analysis. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during Part 1: Treatment Period 2. Analysis was performed on FAS for Part 2. Here, "n" signifies those subjects who were evaluable for this endpoint at specified time-point.

End point type	Secondary

End point timeframe:

Baseline (pre-dose Week 12), Week 36

End point values	Part 1 Treatment Period 2: Ivacaftor, Part 2: OLE Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (n=18) Change at Week 36 (n=17)	92.03 (± 11.468) -59.24 (± 32.566)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 8

End point title	Part 1: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 8

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms (for example, coughing, congestion, wheezing), score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during study Part 1. Analysis was performed on FAS for Part 1.

End point type	Secondary

End point timeframe:

Part 1: Baseline through Week 8

End point values	Part 1: Ivacaftor	Part 1: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: units on a scale				
least squares mean (standard error)	8.9385 (± 1.8178)	-0.672 (± 1.8475)		

Attachments (see zip file)	Statistical Analysis/Part 1 - Absolute Change From Baseline in

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absolute Change From Baseline in CFQ-R Respiratory Domain Score at 24 Weeks of Treatment (Week 36 Visit)

End point title	Part 2: Absolute Change From Baseline in CFQ-R Respiratory Domain Score at 24 Weeks of Treatment (Week 36 Visit)

End point description:

The CFQ-R and CFQ-R respiratory domain are defined in Part 1 endpoint. Absolute change in CFQ-R respiratory domain score at 24 weeks of ivacaftor treatment (from Week 12 [Part 1: Treatment Period 2] at Week 36 [Part 2]) was reported for subjects who received ivacaftor in Part 1: Treatment Period 2 as per planned analysis. Baseline was defined as the most recent non-missing measurement collected before initial administration of study drug during Part 1: Treatment Period 2. Analysis was performed on FAS for Part 2.

End point type	Secondary

End point timeframe:

Baseline (pre-dose Week 12), Week 36

End point values	Part 1 Treatment Period 2: Ivacaftor, Part 2: OLE Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	71.3 (± 19.526)			
Change at Week 36	11.42 (± 13.604)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Number of subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part 1: Number of subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AE: any adverse change from subject's baseline (pre-treatment) condition, including any adverse experience, abnormal recording/clinical laboratory assessment which occurs during course of study, whether it is considered related to study drug or not. SAE: medical event or condition, which falls into any of following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolonged hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect, important medical event. Safety Set for Part 1 included all subjects who received at least 1 dose of study drug (ivacaftor or placebo).

End point type	Secondary

End point timeframe:

Part 1: From signing of informed consent up to Week 20

End point values	Part 1: Ivacaftor	Part 1: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: subjects				
number (not applicable)				
AEs	28	31		
SAEs	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number ofsubjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part 2: Number ofsubjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AE: any adverse change from subject's baseline (pre-treatment) condition, including any adverse experience, abnormal recording/clinical laboratory assessment which occurs during course of study, whether it is considered related to study drug or not. SAE: medical event or condition, which falls into any of following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolonged hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect, important medical event. Safety Set for Part 2 included all subjects who received at least 1 dose of study drug (ivacaftor).

End point type	Secondary

End point timeframe:

Part 2: Week 20 up to Week 40

End point values	Open-label Extension (OLE) Ivacaftor			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: subjects				
number (not applicable)				
AEs	30			
SAEs	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Part 1: From signing of informed consent up to Week 20; Part 2: Week 20 up to Week 40	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Part 1: Placebo
Reporting group description: Placebo matched to ivacaftor tablet orally twice daily for 8 weeks in either Sequence 1 or Sequence 2.	
Reporting group title	Part 1: Ivacaftor
Reporting group description: Ivacaftor 150 mg tablet orally twice daily for 8 weeks in either Sequence 1 or Sequence 2.	
Reporting group title	Part 2: OLE Ivacaftor
Reporting group description: Ivacaftor 150 mg tablet orally twice daily for 16 weeks.	

Serious adverse events	Part 1: Placebo	Part 1: Ivacaftor	Part 2: OLE Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)	4 / 38 (10.53%)	3 / 36 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (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
Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (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
Gastrointestinal disorders			
Distal ileal obstruction syndrome			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Appendiceal mucocoele			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (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
Intussusception			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (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
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (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
Respiratory, thoracic and mediastinal disorders			
Paranasal cyst			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (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			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	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
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	6 / 37 (16.22%)	2 / 38 (5.26%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (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: 0 %

Non-serious adverse events	Part 1: Placebo	Part 1: Ivacaftor	Part 2: OLE Ivacaftor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 37 (81.08%)	27 / 38 (71.05%)	30 / 36 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oral papilloma			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Malignant melanoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 38 (7.89%)	2 / 36 (5.56%)
occurrences (all)	1	3	2
Exercise tolerance decreased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 37 (0.00%)	2 / 38 (5.26%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Chest pain			

subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Medical device site reaction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Infusion site thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal discomfort			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Sputum increased			
subjects affected / exposed	3 / 37 (8.11%)	3 / 38 (7.89%)	2 / 36 (5.56%)
occurrences (all)	3	3	2
Cough			
subjects affected / exposed	7 / 37 (18.92%)	6 / 38 (15.79%)	5 / 36 (13.89%)
occurrences (all)	10	6	7
Dysphonia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	0	1	1
Haemoptysis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	2	1	1
Lung hyperinflation			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	1	1	1
Nasal congestion			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal pain			
subjects affected / exposed	3 / 37 (8.11%)	1 / 38 (2.63%)	3 / 36 (8.33%)
occurrences (all)	4	1	3
Rales			
subjects affected / exposed	3 / 37 (8.11%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	3	1	1
Rhinorrhoea			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Respiration abnormal			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	2 / 36 (5.56%)
occurrences (all)	0	1	2

Asthma			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	3 / 36 (8.33%)
occurrences (all)	1	0	4
Bronchospasm			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nasal mucosal disorder			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Productive cough			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Pulmonary congestion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Sputum discoloured			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Respiratory tract congestion			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Sinus congestion			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	2 / 36 (5.56%)
occurrences (all)	3	0	2
Nasal polyps			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Vocal cord inflammation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1

Pneumonitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Neutrophil count increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Respiratory rate increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Breath sounds abnormal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Pulmonary function test decreased			

subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	2
Weight decreased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Arthropod bite			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Vaccination complication			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	5 / 37 (13.51%)	3 / 38 (7.89%)	4 / 36 (11.11%)
occurrences (all)	6	5	8
Lethargy			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Sinus headache			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Benign intracranial hypertension			

subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Cerumen impaction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Hypoacusis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 37 (2.70%)	2 / 38 (5.26%)	2 / 36 (5.56%)
occurrences (all)	1	2	2
Abdominal pain			
subjects affected / exposed	4 / 37 (10.81%)	1 / 38 (2.63%)	3 / 36 (8.33%)
occurrences (all)	4	1	3
Distal ileal obstruction syndrome			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Toothache			

subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	4 / 37 (10.81%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	4	1	1
Cheilitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Abdominal distension			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Anal fissure			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Food poisoning			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1

Pancreatitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	1 / 36 (2.78%)
occurrences (all)	2	2	1
Dermatitis contact			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	1 / 37 (2.70%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Rash papular			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Thyroid disorder			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 37 (0.00%)	2 / 38 (5.26%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Back pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Torticollis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Osteochondrosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Pain in jaw			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	6 / 37 (16.22%)	7 / 38 (18.42%)	4 / 36 (11.11%)
occurrences (all)	8	8	4
Rhinitis			
subjects affected / exposed	2 / 37 (5.41%)	3 / 38 (7.89%)	0 / 36 (0.00%)
occurrences (all)	2	3	0
Conjunctivitis infective			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	2 / 37 (5.41%)	2 / 38 (5.26%)	0 / 36 (0.00%)
occurrences (all)	2	2	0
Sinusitis			

subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	2 / 36 (5.56%)
occurrences (all)	2	1	2
Respiratory tract infection viral			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	3 / 36 (8.33%)
occurrences (all)	2	2	3
Bronchitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Bacterial disease carrier			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Tonsillitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Gastrointestinal viral infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Impetigo			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			

subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Decreased appetite			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2012	The ppFEV1 inclusion criterion updated.
21 March 2012	Study assessments and exclusion criteria updated, Part 2 statistical methodology clarified.
07 September 2012	Observational arm eligibility criteria, screening assessments and study assessments updated.
05 December 2012	Study assessments clarified.

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 of Part 1.

Notes: