

**Clinical trial results:****A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who are 2 Through 5 Years of Age and Have a CFTR Gating Mutation**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

**Summary**

EudraCT number	2012-000204-15
Trial protocol	GB
Global end of trial date	18 March 2014

**Results information**

Result version number	v2 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Edit to address EudraCT bug related issues & also data errors

**Trial information****Trial identification**

Sponsor protocol code	VX11-770-108
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01705145
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, MA, United States, 02210-1862
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	26 June 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 March 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD), of ivacaftor in children with cystic fibrosis (CF) who are 2 through 5 years of age and have a CF Transmembrane Conductance Regulator (CFTR) gating mutation in at least 1 allele.

Part A is designed to evaluate the safety and PK of multiple-dose administration of ivacaftor in subjects 2 through 5 years of age and to confirm the doses for Part B. Part B is designed to evaluate the safety, PK, PD, and efficacy of ivacaftor in subjects 2 through 5 years of age.

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	08 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	20 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	35
EEA total number of subjects	8

Notes:

### Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	35
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

For Part A: a total of 11 subjects were screened, of whom 9 subjects were enrolled. For Part B: a total of 37 subjects were screened, of whom 34 subjects were enrolled (eight of the 9 subjects who participated in Part A were enrolled in Part B).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Part A: Ivacaftor 50 mg

Arm description:

Ivacaftor 50 milligram (mg) (for subjects weighing less than [ $<$ ] 14 kilograms [kg]) every 12 hours (q12h) from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

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

Dosage and administration details:

Ivacaftor 50 mg (for subjects weighing  $<14$  kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

<b>Arm title</b>	Part A: Ivacaftor 75 mg
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Arm description:

Ivacaftor 75 mg (for subjects weighing  $\geq 14$  kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

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

Dosage and administration details:

Ivacaftor 75 mg (for subjects weighing  $\geq 14$  kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

<b>Arm title</b>	Part B: Ivacaftor 50 mg
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Arm description:

Ivacaftor 50 mg (for subjects weighing  $<14$  kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

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

Dosage and administration details:

Ivacaftor 50 mg (for subjects weighing <14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

<b>Arm title</b>	Part B: Ivacaftor 75 mg
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Arm description:

Ivacaftor 75 mg (for subjects weighing ≥14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

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

Dosage and administration details:

Ivacaftor 75 mg (for subjects weighing ≥14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

<b>Number of subjects in period 1</b>	Part A: Ivacaftor 50 mg	Part A: Ivacaftor 75 mg	Part B: Ivacaftor 50 mg
Started	4	5	10
Completed	4	5	9
Not completed	0	0	1
Adverse Event	-	-	1

<b>Number of subjects in period 1</b>	Part B: Ivacaftor 75 mg
Started	24
Completed	24
Not completed	0
Adverse Event	-

## Baseline characteristics

### Reporting groups

Reporting group title	Part A: Ivacaftor 50 mg
Reporting group description: Ivacaftor 50 milligram (mg) (for subjects weighing less than [ $<$ ] 14 kilograms [kg]) every 12 hours (q12h) from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.	
Reporting group title	Part A: Ivacaftor 75 mg
Reporting group description: Ivacaftor 75 mg (for subjects weighing $\geq$ 14 kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.	
Reporting group title	Part B: Ivacaftor 50 mg
Reporting group description: Ivacaftor 50 mg (for subjects weighing $<$ 14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.	
Reporting group title	Part B: Ivacaftor 75 mg
Reporting group description: Ivacaftor 75 mg (for subjects weighing $\geq$ 14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.	

Reporting group values	Part A: Ivacaftor 50 mg	Part A: Ivacaftor 75 mg	Part B: Ivacaftor 50 mg
Number of subjects	4	5	10
Age categorical Units: Subjects			
Children (2-11 years)	4	5	10
Age Continuous Units: years			
arithmetic mean	2.3	3.8	2.3
standard deviation	$\pm 0.5$	$\pm 1.1$	$\pm 0.48$
Gender categorical Units: Subjects			
Female	2	1	4
Male	2	4	6

Reporting group values	Part B: Ivacaftor 75 mg	Total	
Number of subjects	24	35	
Age categorical Units: Subjects			
Children (2-11 years)	24	35	
Age Continuous Units: years			
arithmetic mean	3.6	-	
standard deviation	$\pm 0.82$		
Gender categorical Units: Subjects			
Female	2	7	
Male	22	28	

## End points

### End points reporting groups

Reporting group title	Part A: Ivacaftor 50 mg
Reporting group description: Ivacaftor 50 milligram (mg) (for subjects weighing less than [ $<$ ] 14 kilograms [kg]) every 12 hours (q12h) from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.	
Reporting group title	Part A: Ivacaftor 75 mg
Reporting group description: Ivacaftor 75 mg (for subjects weighing $\geq 14$ kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.	
Reporting group title	Part B: Ivacaftor 50 mg
Reporting group description: Ivacaftor 50 mg (for subjects weighing $< 14$ kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.	
Reporting group title	Part B: Ivacaftor 75 mg
Reporting group description: Ivacaftor 75 mg (for subjects weighing $\geq 14$ kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.	
Subject analysis set title	Part B: Overall Ivacaftor
Subject analysis set type	Full analysis
Subject analysis set description: Ivacaftor 50 mg (for subjects weighing $< 14$ kg) or 75 mg (for subjects weighing $\geq 14$ kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.	
Subject analysis set title	Part A: Overall Ivacaftor
Subject analysis set type	Full analysis
Subject analysis set description: Ivacaftor 50 mg (for subjects weighing $< 14$ kg) or 75 mg (for subjects weighing $\geq 14$ kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.	

### Primary: Part A: Number of subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and Related AEs

End point title	Part A: Number of subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and Related AEs <sup>[1][2]</sup>
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. Related AEs includes all AEs for which the causality was either related to study drug or possibly related to study drug.  Part A Safety set included all subjects who received at least 1 dose of study drug in part A.	
End point type	Primary
End point timeframe: Part A: Up to 93 Days	
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: No statistical analysis was planned for this endpoint. [2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is not reporting the data for all arms because Part A and Part B endpoints are reported separately and hence, this endpoint includes only those arms which are applicable for the Part specified in endpoint title.	

End point values	Part A: Ivacaftor 50 mg	Part A: Ivacaftor 75 mg	Part A: Overall Ivacaftor	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	5	9	
Units: subjects				
number (not applicable)				
AEs	3	5	8	
SAEs	0	0	0	
Related AEs	1	3	4	

## Statistical analyses

No statistical analyses for this end point

## Primary: Part B: Number of subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and Related AEs

End point title	Part B: Number of subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and Related AEs <sup>[3][4]</sup>
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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. AE includes both serious and non-serious AE. 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. Related AEs includes all AEs for which the causality was either related to study drug or possibly related to study drug.

Part B Safety set included all subjects who received at least 1 dose of study drug in part B.

End point type	Primary
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End point timeframe:

Part B: Up to 28 Weeks

Notes:

[3] - 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 this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint is not reporting the data for all arms because Part A and Part B endpoints are reported separately and hence, this endpoint includes only those arms which are applicable for the Part specified in endpoint title.

End point values	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	24	34	
Units: subjects				
number (not applicable)				
AEs	10	23	33	
SAEs	3	3	6	
Related AEs	3	8	11	



## Statistical analyses

No statistical analyses for this end point

### Primary: Part A: Plasma Concentration of Ivacaftor and its Metabolites

End point title	Part A: Plasma Concentration of Ivacaftor and its Metabolites <sup>[5]</sup>
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End point description:

Plasma concentration was reported for ivacaftor and its metabolites (hydroxymethyl ivacaftor [M1] and ivacaftor carboxylate [M6]) up to 24 hours post-dose on Day 4 (Hour 0 [pre-dose] on Day 1 and Day 4; 2, 3, 6, 24 hours post-dose on Day 4). Data was planned to be reported for overall subjects in the period.

Part A Safety set included all subjects who received at least 1 dose of study drug in part A.

End point type	Primary
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End point timeframe:

Part A: up to 24 hours post-dose on Day 4

Notes:

[5] - 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 this endpoint.

End point values	Part A: Overall Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Ivacaftor: Hour 0 on Day 1	0 (± 0)			
Ivacaftor: Hour 0 on Day 4	396 (± 337)			
Ivacaftor: 2 Hours Post-Dose on Day 4	726 (± 284)			
Ivacaftor: 3 Hours Post-Dose on Day 4	957 (± 283)			
Ivacaftor: 6 Hours Post-Dose on Day 4	542 (± 241)			
Ivacaftor: 24 Hours Post-Dose on Day 4	124 (± 149)			
M1: Hour 0 on Day 1	0 (± 0)			
M1: Hour 0 on Day 4	1240 (± 723)			
M1: 2 Hours Post-Dose on Day 4	1540 (± 578)			
M1: 3 Hours Post-Dose on Day 4	2310 (± 820)			
M1: 6 Hours Post-Dose on Day 4	1580 (± 622)			
M1: 24 Hours Post-Dose on Day 4	389 (± 336)			
M6: Hour 0 on Day 1	0 (± 0)			
M6: Hour 0 on Day 4	1150 (± 709)			
M6: 2 Hours Post-Dose on Day 4	1050 (± 606)			
M6: 3 Hours Post-Dose on Day 4	1300 (± 614)			
M6: 6 Hours Post-Dose on Day 4	1390 (± 532)			
M6: 24 Hours Post-Dose on Day 4	439 (± 355)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Plasma Concentration of Ivacaftor and its Metabolites

End point title	Part B: Plasma Concentration of Ivacaftor and its Metabolites
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End point description:

Plasma concentration was reported for ivacaftor and its metabolites (M1 and M6) up to 24 hours post-dose on Day 168 (Hour 0 [predose] on Day 1, 14, 56, 112, and 168; 2, 3, 6 hours post-dose on Day 14; 1 hour post-dose on Day 56; 4, 6 hours post-dose on Day 112; 24 hours post-dose on Day 168). Data was planned to be reported for overall subjects in the period.

Part B Safety set included all subjects who received at least 1 dose of study drug in part B.

End point type	Secondary
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End point timeframe:

Part B: up to 24 hours post-dose on Day 168

End point values	Part B: Overall Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: ng/mL				
arithmetic mean (standard deviation)				
Ivacaftor: Hour 0 on Day 1	0 (± 0)			
Ivacaftor: Hour 0 on Day 14	614 (± 590)			
Ivacaftor: 2 Hours Post-Dose on Day 14	932 (± 541)			
Ivacaftor: 3 Hours Post-Dose on Day 14	1080 (± 587)			
Ivacaftor: 6 Hours Post-Dose on Day 14	1140 (± 627)			
Ivacaftor: Hour 0 on Day 56	448 (± 455)			
Ivacaftor: 1 Hour Post-Dose on Day 56	514 (± 421)			
Ivacaftor: Hour 0 on Day 112	596 (± 747)			
Ivacaftor: 4 Hours Post-Dose on Day 112	1080 (± 835)			
Ivacaftor: 6 Hours Post-Dose on Day 112	1010 (± 885)			
Ivacaftor: Hour 0 on Day 168	500 (± 545)			
Ivacaftor: 24 Hours Post-Dose on Day 168	207 (± 372)			
M1: Hour 0 on Day 1	0 (± 0)			
M1: Hour 0 on Day 14	1580 (± 1030)			
M1: 2 Hours Post-Dose on Day 14	1870 (± 924)			
M1: 3 Hours Post-Dose on Day 14	2280 (± 1140)			
M1: 6 Hours Post-Dose on Day 14	2670 (± 1080)			
M1: Hour 0 on Day 56	1340 (± 880)			
M1: 1 Hour Post-Dose on Day 56	1170 (± 698)			

M1: Hour 0 on Day 112	1680 ( $\pm$ 1360)			
M1: 4 Hours Post-Dose on Day 112	2450 ( $\pm$ 1510)			
M1: 6 Hours Post-Dose on Day 112	2500 ( $\pm$ 1520)			
M1: Hour 0 on Day 168	1460 ( $\pm$ 1200)			
M1: 24 Hours Post-Dose on Day 168	602 ( $\pm$ 647)			
M6: Hour 0 on Day 1	0 ( $\pm$ 0)			
M6: Hour 0 on Day 14	1520 ( $\pm$ 1130)			
M6: 2 Hours Post-Dose on Day 14	1430 ( $\pm$ 989)			
M6: 3 Hours Post-Dose on Day 14	1630 ( $\pm$ 1130)			
M6: 6 Hours Post-Dose on Day 14	2090 ( $\pm$ 1350)			
M6: Hour 0 on Day 56	1510 ( $\pm$ 1080)			
M6: 1 Hour Post-Dose on Day 56	1310 ( $\pm$ 974)			
M6: Hour 0 on Day 112	1660 ( $\pm$ 1130)			
M6: 4 Hours Post-Dose on Day 112	1810 ( $\pm$ 1230)			
M6: 6 Hours Post-Dose on Day 112	2130 ( $\pm$ 1380)			
M6: Hour 0 on Day 168	1520 ( $\pm$ 1130)			
M6: 24 Hours Post-Dose on Day 168	632 ( $\pm$ 465)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Absolute Change from Baseline in Sweat Chloride at Week 24

End point title	Part B: Absolute Change from Baseline in Sweat Chloride at Week 24 <sup>[6]</sup>
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End point description:

Sweat samples were collected using an approved Macroduct (Wescor, Logan, Utah) collection device. A volume of greater than or equal to ( $\geq$ ) 15 microliter was required for determination of sweat chloride. Data was reported as per the dose received and for overall subjects.

Part B Safety set included all subjects who received at least 1 dose of study drug in part B. Number of subjects analyzed is for subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Part B: Baseline, Week 24

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is not reporting the data for all arms because Part A and Part B endpoints are reported separately and hence, this endpoint includes only those arms which are applicable for the Part specified in endpoint title.

End point values	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7	18	25	
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)	-47.07 ( $\pm$ 24.256)	-46.78 ( $\pm$ 27.584)	-46.86 ( $\pm$ 26.193)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Absolute Change from Baseline in Weight at Week 24

End point title	Part B: Absolute Change from Baseline in Weight at Week 24 <sup>[7]</sup>
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End point description:

Data was reported as per the dose received and for overall subjects.

Part B Safety set included all subjects who received at least 1 dose of study drug in part B. Number of subjects analyzed is for subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Part B: Baseline, Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is not reporting the data for all arms because Part A and Part B endpoints are reported separately and hence, this endpoint includes only those arms which are applicable for the Part specified in endpoint title.

End point values	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	24	33	
Units: kilograms (kg)				
arithmetic mean (standard deviation)	1 (± 0.418)	1.5 (± 0.552)	1.36 (± 0.561)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Absolute Change from Baseline in Stature at Week 24

End point title	Part B: Absolute Change from Baseline in Stature at Week 24 <sup>[8]</sup>
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End point description:

Stature was measured as height if children could stand unassisted and follow directions; otherwise, stature was measured as length. Data was reported as per the dose received and for overall subjects.

Part B Safety set included all subjects who received at least 1 dose of study drug in part B. Number of subjects analyzed is for subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Part B: Baseline, Week 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is not reporting the data for all arms because Part A and Part B endpoints are reported separately and hence, this endpoint includes only those arms which are applicable for the Part specified in endpoint title.

End point values	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	23	32	
Units: centimeters (cm)				
arithmetic mean (standard deviation)	2.5 (± 1.45)	3.5 (± 0.93)	3.3 (± 1.17)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: Absolute Change from Baseline in Body Mass Index (BMI) at Week 24

End point title	Part B: Absolute Change from Baseline in Body Mass Index (BMI) at Week 24 <sup>[9]</sup>
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End point description:

BMI = (Weight [in kg]) divided by (Stature [in meters])<sup>2</sup>. Data was reported as per the dose received and for overall subjects.

Part B Safety set included all subjects who received at least 1 dose of study drug in part B. Number of subjects analyzed is for subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is not reporting the data for all arms because Part A and Part B endpoints are reported separately and hence, this endpoint includes only those arms which are applicable for the Part specified in endpoint title.

End point values	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	23	32	
Units: kilogram per square meter (kg/m <sup>2</sup> )				
arithmetic mean (standard deviation)	0.332 (± 0.5393)	0.314 (± 0.5492)	0.319 (± 0.5378)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Part A: up to 93 days; Part B: up to 28 weeks

Adverse event reporting additional description:

Adverse events were reported separately for each part and as per the dose received and for overall subjects in each part.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Part A: Ivacaftor 50 mg
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Reporting group description:

Ivacaftor 50 mg (for subjects weighing <14 kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

Reporting group title	Part A: Ivacaftor 75 mg
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Reporting group description:

Ivacaftor 75 mg (for subjects weighing ≥14 kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

Reporting group title	Part A: Overall Ivacaftor
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Reporting group description:

Ivacaftor 50 mg (for subjects weighing <14 kg) or 75 mg (for subjects weighing ≥14 kg) q12h from Day 1 through Day 3 and 1 morning dose on Day 4 during Part A of the study.

Reporting group title	Part B: Ivacaftor 50 mg
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Reporting group description:

Ivacaftor 50 mg (for subjects weighing <14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

Reporting group title	Part B: Ivacaftor 75 mg
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Reporting group description:

Ivacaftor 75 mg (for subjects weighing ≥14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

Reporting group title	Part B: Overall Ivacaftor
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Reporting group description:

Ivacaftor 50 mg (for subjects weighing <14 kg) or 75 mg (for subjects weighing ≥14 kg) q12h for 24 weeks during Part B of the study. Part B included subjects from Part A and newly enrolled subjects.

Serious adverse events	Part A: Ivacaftor 50 mg	Part A: Ivacaftor 75 mg	Part A: Overall Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Pseudomonas test positive			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	3 / 24 (12.50%)	6 / 34 (17.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Pseudomonas test positive			

subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 24 (4.17%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
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 A: Ivacaftor 50 mg	Part A: Ivacaftor 75 mg	Part A: Overall Ivacaftor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	5 / 5 (100.00%)	8 / 9 (88.89%)
General disorders and administration site conditions			



Pyrexia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 5 (40.00%)	4 / 9 (44.44%)
occurrences (all)	2	2	4
Application site rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Product taste abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nasal inflammation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Snoring			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Pancreatic enzymes increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Bacterial test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Haemophilus test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Antibiotic resistant Staphylococcus test positive			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory rate increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Staphylococcus test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Face injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Mouth injury			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Open wound subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Traumatic haemorrhage subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	1 / 9 (11.11%) 1
Drooling subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Sinus headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Eye disorders Amblyopia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Anisometropia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Eye inflammation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Eruclation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lip blister			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oral mucosal erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Teething			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Ecchymosis			

subjects affected / exposed	0 / 4 (0.00%)	2 / 5 (40.00%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Rash macular			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Genital candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hand-foot-and-mouth disease			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infectious mononucleosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Viral rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Weight gain poor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

<b>Non-serious adverse events</b>	Part B: Ivacaftor 50 mg	Part B: Ivacaftor 75 mg	Part B: Overall Ivacaftor
Total subjects affected by non-serious adverse events			



subjects affected / exposed	9 / 10 (90.00%)	23 / 24 (95.83%)	32 / 34 (94.12%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 10 (40.00%)	2 / 24 (8.33%)	6 / 34 (17.65%)
occurrences (all)	5	3	8
Application site rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 24 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Product taste abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 24 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 10 (20.00%)	5 / 24 (20.83%)	7 / 34 (20.59%)
occurrences (all)	2	7	9
Cough			
subjects affected / exposed	4 / 10 (40.00%)	15 / 24 (62.50%)	19 / 34 (55.88%)
occurrences (all)	8	29	37
Upper respiratory tract congestion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	2	2
Nasal congestion			
subjects affected / exposed	4 / 10 (40.00%)	5 / 24 (20.83%)	9 / 34 (26.47%)
occurrences (all)	6	5	11
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	3 / 24 (12.50%)	3 / 34 (8.82%)
occurrences (all)	0	3	3
Dyspnoea exertional			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1

Nasal inflammation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 24 (4.17%) 1	1 / 34 (2.94%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 24 (4.17%) 1	1 / 34 (2.94%) 1
Snoring subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 24 (4.17%) 1	1 / 34 (2.94%) 1
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 24 (0.00%) 0	1 / 34 (2.94%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 24 (4.17%) 2	1 / 34 (2.94%) 2
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 24 (4.17%) 2	1 / 34 (2.94%) 2
Pancreatic enzymes increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 24 (0.00%) 0	0 / 34 (0.00%) 0
Bacterial test positive subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 24 (12.50%) 3	3 / 34 (8.82%) 3
Haemophilus test positive subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 24 (12.50%) 4	3 / 34 (8.82%) 4
Hepatic enzyme increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4	0 / 24 (0.00%) 0	2 / 34 (5.88%) 4
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 24 (0.00%) 0	1 / 34 (2.94%) 1
Antibiotic resistant Staphylococcus test positive			

subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Blood creatine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Lymphocyte count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	2	2
Respiratory rate increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	2
Staphylococcus test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	2	2
White blood cell count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Face injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Mouth injury			

subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Open wound			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Traumatic haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Upper limb fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Drooling			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Sinus headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	2	2
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Anisometropia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Eye inflammation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	3 / 10 (30.00%)	6 / 24 (25.00%)	9 / 34 (26.47%)
occurrences (all)	3	6	9
Abdominal distension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	4 / 24 (16.67%)	4 / 34 (11.76%)
occurrences (all)	0	4	4
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 24 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Eruclation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Lip blister			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Oral mucosal erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Retching			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Teething			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	3
Skin and subcutaneous tissue disorders			
Ecchymosis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 24 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 24 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 10 (20.00%)	2 / 24 (8.33%)	4 / 34 (11.76%)
occurrences (all)	2	4	6
Acne			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Dermatitis contact			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Petechiae			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Skin irritation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Pollakiuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Pain in extremity			

subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 24 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	7 / 24 (29.17%)	8 / 34 (23.53%)
occurrences (all)	1	12	13
Croup infectious			
subjects affected / exposed	2 / 10 (20.00%)	1 / 24 (4.17%)	3 / 34 (8.82%)
occurrences (all)	2	1	3
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 10 (0.00%)	3 / 24 (12.50%)	3 / 34 (8.82%)
occurrences (all)	0	4	4
Otitis media			
subjects affected / exposed	2 / 10 (20.00%)	1 / 24 (4.17%)	3 / 34 (8.82%)
occurrences (all)	2	1	3
Sinusitis			
subjects affected / exposed	2 / 10 (20.00%)	1 / 24 (4.17%)	3 / 34 (8.82%)
occurrences (all)	2	1	3
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Bacterial disease carrier			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Genital candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Hand-foot-and-mouth disease			

subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Infectious mononucleosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Lung infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Pharyngitis streptococcal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	2
Respiratory tract infection viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Viral rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 10 (10.00%)	1 / 24 (4.17%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Weight gain poor			
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2012	Changed inclusion criterion to allow subjects older than 5 years of age at entry in Part B to enter Part B from Part A. Added ophthalmologic examinations. Study design was modified to state that all subjects in Part B were to be enrolled in VX11-770-109 (Study 109). Modified secondary endpoints for analysis of PK parameters (remove duration of treatment) and of weight, stature, and BMI to be "through 24 weeks".
02 November 2012	Changed required components of ophthalmologic examinations. Aligned requirement for all subjects who prematurely discontinue treatment in Part B to enroll in the observational arm of VX11-770-109 (Study 109). Aligned food requirement for study drug administration to more closely align with approved product labeling.
09 November 2012	The reference evaluation scale was changed to the Lens Opacities Classification System III (LOCS III) grading scale.
08 May 2013	Removed upper limit on the number of subjects in Part B. Added text to specify that the data monitoring committee (DMC), should be notified if a lens opacity or cataract is identified. Modified prohibited medications to restrict only moderate and strong inhibitors and inducers of cytochrome P4503A (CYP3A). Added urinalysis screening assessment to the Part B Schedule of Assessments.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported