



Clinical trial results:

A Phase 3, 2-Arm, Roll-Over Study to Evaluate the Long-term Safety and Pharmacodynamics of Ivacaftor Treatment in Pediatric Subjects With Cystic Fibrosis and a CFTR Gating Mutation

Summary

EudraCT number	2012-000386-20
Trial protocol	GB
Global end of trial date	17 December 2015

Results information

Result version number	v1 (current)
This version publication date	02 July 2016
First version publication date	02 July 2016

Trial information

Trial identification

Sponsor protocol code	VX11-770-109
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01946412
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, +1 617-341-6777, 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of ivacaftor treatment.

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	16 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	European Union: 8
Worldwide total number of subjects	33
EEA total number of subjects	0

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)	33
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:

This was a Phase 3, multicenter, 2 arm study in subjects who received at least 1 dose of study drug in parent study VX11-770-108 (study 108) (2012-000204-15).

Pre-assignment

Screening details:

In study VX11-770-109 (study 109) (2012-000386-20), subjects were to be enrolled in either ivacaftor arm or observational arm. However, there were no subjects enrolled in the observational arm. A total of 33 subjects were enrolled in the ivacaftor arm.

Period 1

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

Arms

Arm title	Ivacaftor
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Arm description:

Subjects received ivacaftor 50 milligram (mg) or 75 mg or 150 mg based on body weight and age. Ivacaftor 50 mg administered every 12 hours (q12h) for subjects aged 2 to less than (<) 6 years and weighing <14 kilograms (kg), ivacaftor 75 mg q12h for subjects aged 2 to <6 years and weighing greater than or equal to (>=) 14 kg and ivacaftor 150 mg q12h for subjects >=6 years.

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

Dosage and administration details:

Subjects received either ivacaftor 50 mg or 75 mg or 150 mg orally q12h. Mini-tablets were used for 50 and 75 mg doses and tablet for 150 mg dose.

Number of subjects in period 1	Ivacaftor
Started	33
Completed	28
Not completed	5
Non-Compliance	1
Adverse Event	1
Difficulty in swallowing	1
Continued with commercial Kalydeco	2

Baseline characteristics

Reporting groups

Reporting group title	Ivacaftor
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Reporting group description:

Subjects received ivacaftor 50 milligram (mg) or 75 mg or 150 mg based on body weight and age. Ivacaftor 50 mg administered every 12 hours (q12h) for subjects aged 2 to less than (<) 6 years and weighing <14 kilograms (kg), ivacaftor 75 mg q12h for subjects aged 2 to <6 years and weighing greater than or equal to (>=) 14 kg and ivacaftor 150 mg q12h for subjects >=6 years.

Reporting group values	Ivacaftor	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	3.7 ± 1.04	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	27	27	

End points

End points reporting groups

Reporting group title	Ivacaftor
Reporting group description: Subjects received ivacaftor 50 milligram (mg) or 75 mg or 150 mg based on body weight and age. Ivacaftor 50 mg administered every 12 hours (q12h) for subjects aged 2 to less than (<) 6 years and weighing <14 kilograms (kg), ivacaftor 75 mg q12h for subjects aged 2 to <6 years and weighing greater than or equal to (>=) 14 kg and ivacaftor 150 mg q12h for subjects >=6 years.	
Subject analysis set title	Ivacaftor 50 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received ivacaftor 50 mg q12h in parent study VX11-770-108 (2012-000204-15), received either ivacaftor 50 mg q12h for subjects aged 2 to <6 years and weighing <14 kg or ivacaftor 75 mg q12h for subjects aged 2 to <6 years and >=14 kg or ivacaftor 150 mg q12h for subjects >=6 years in this study (2012-000386-20).	
Subject analysis set title	Ivacaftor 75 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received ivacaftor 75 mg q12h in parent study VX11-770-108 (2012-000204-15), received either ivacaftor 50 mg q12h for subjects aged 2 to <6 years and weighing <14 kg or ivacaftor 75 mg q12h for subjects aged 2 to <6 years and >=14 kg or ivacaftor 150 mg q12h for subjects >=6 years in this study (2012-000386-20).	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
End point description: AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed. AE includes serious as well as Non-serious AEs. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, Inpatient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. AEs with start date on or after the first dose of study drug through the end of study participation was considered treatment-emergent. Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20).	
End point type	Primary
End point timeframe: Day 1 up to Week 97 (for subjects who completed study drug dosing); Day 1 up to 24 weeks after the last dose of study drug (up to Week 108, for subjects who prematurely discontinued study drug dosing).	

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: Only descriptive statistics were reported, inferential statistics were not planned for primary endpoint.

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[2]	24 ^[3]		
Units: Subjects				
Subjects with SAEs	6	5		
Subjects with AEs	9	24		

Notes:

[2] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[3] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Parent Study in Sweat Chloride at Week 24, 48, 72 and 84

End point title	Absolute Change From Baseline of Parent Study in Sweat Chloride at Week 24, 48, 72 and 84
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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. Baseline was defined as the most recent measurement prior to intake of the first dose of study drug in study 108 Part B (2012-000204-15). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (study 108), Week 24, 48, 72 and 84 (study 109)

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[4]	24 ^[5]		
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Baseline (n=7,22)	93.1 (\pm 16.2)	99.6 (\pm 13.6)		
Absolute Change at Week 24 (n=6,18)	-62.1 (\pm 12.4)	-48.5 (\pm 18.4)		
Absolute Change at Week 48 (n=6,15)	-29.3 (\pm 37.8)	-51.8 (\pm 27.1)		
Absolute Change at Week 72 (n=7,14)	-46.4 (\pm 16)	-52.9 (\pm 26.7)		
Absolute Change at Week 84 (n=6,14)	-46.5 (\pm 31)	-58.1 (\pm 23.9)		

Notes:

[4] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[5] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Study 109 in Sweat Chloride at Week 24, 48, 72 and 84

End point title	Absolute Change From Baseline of Study 109 in Sweat Chloride at Week 24, 48, 72 and 84
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End point description:

Sweat samples were collected using an approved Macroduct (Wescor, Logan, Utah) collection device. A

volume of ≥ 15 microliter was required for determination of sweat chloride. Baseline is defined as the most recent measurement prior to intake of the first dose of study drug in study 109 (2012-000386-20). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
End point timeframe:	
Baseline (study 109), Week 24, 48, 72 and 84 (study 109)	

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[6]	24 ^[7]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (n= 8,23)	47.8 (\pm 23.3)	52.9 (\pm 23.1)		
Absolute Change at Week 24 (n=7,18)	-4.3 (\pm 31.6)	3.4 (\pm 15.9)		
Absolute Change at Week 48 (n=7,17)	18.1 (\pm 39.5)	-4.5 (\pm 22.6)		
Absolute Change at Week 72 (n=8,15)	-1.5 (\pm 24.3)	-6 (\pm 20.8)		
Absolute Change at Week 84 (n=7,16)	-2.4 (\pm 44.2)	-11.2 (\pm 25.4)		

Notes:

[6] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[7] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Parent Study in Weight at Week 12, 24, 36, 48, 60, 72 and 84

End point title	Absolute Change From Baseline of Parent Study in Weight at Week 12, 24, 36, 48, 60, 72 and 84
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End point description:

Baseline was defined as the most recent measurement prior to intake of the first dose of study drug in study 108 Part B (2012-000204-15). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
End point timeframe:	
Baseline (study 108), Week 12, 24, 36, 48, 60, 72 and 84 (study 109)	

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[8]	24 ^[9]		
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline (n=9, 24)	12.5 (\pm 1.1)	16.8 (\pm 1.8)		

Absolute Change at Week 12 (n= 9, 23)	1.3 (± 0.4)	1.9 (± 0.7)		
Absolute Change at Week 24 (n=9, 23)	2 (± 0.6)	2.5 (± 0.9)		
Absolute Change at Week 36 (n=9, 23)	2.4 (± 0.7)	3.1 (± 1)		
Absolute Change at Week 48 (n=9, 22)	2.6 (± 0.9)	3.4 (± 1.1)		
Absolute Change at Week 60 (n=9, 22)	3.2 (± 1)	4 (± 1.3)		
Absolute Change at Week 72 (n=9, 20)	3.4 (± 0.9)	4.8 (± 1.6)		
Absolute Change at Week 84 (n=9, 19)	4 (± 1.2)	5.7 (± 1.9)		

Notes:

[8] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[9] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Study 109 in Weight at Week 12, 24, 36, 48, 60, 72 and 84

End point title	Absolute Change From Baseline of Study 109 in Weight at Week 12, 24, 36, 48, 60, 72 and 84
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End point description:

Baseline is defined as the most recent measurement prior to intake of the first dose of study drug in study 109 (2012-000386-20). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (study 109), Week 12, 24, 36, 48, 60, 72 and 84 (study 109)

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[10]	24 ^[11]		
Units: Kg				
arithmetic mean (standard deviation)				
Baseline (n= 9, 24)	13.5 (± 1)	18.3 (± 2)		
Absolute Change at Week 12 (n=9, 23)	0.3 (± 0.4)	0.4 (± 0.5)		
Absolute Change at Week 24 (n=9, 23)	1 (± 0.5)	1 (± 0.7)		
Absolute Change at Week 36 (n=9, 23)	1.4 (± 0.6)	1.6 (± 0.8)		
Absolute Change at Week 48 (n=9, 22)	1.6 (± 0.7)	1.9 (± 0.8)		
Absolute Change at Week 60 (n=9, 22)	2.2 (± 0.8)	2.5 (± 1.1)		
Absolute Change at Week 72 (n=9, 20)	2.4 (± 0.7)	3.3 (± 1.4)		
Absolute Change at Week 84 (n=9, 19)	3 (± 1)	4.2 (± 1.7)		

Notes:

[10] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[11] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

Secondary: Absolute Change From Baseline of Parent Study in Stature at Week 12, 24, 36, 48, 60, 72 and 84

End point title	Absolute Change From Baseline of Parent Study in Stature at Week 12, 24, 36, 48, 60, 72 and 84
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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. Baseline was defined as the most recent measurement prior to intake of the first dose of study drug in study 108 Part B (2012-000204-15). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (study 108), Week 12, 24, 36, 48, 60, 72 and 84 (study 109)

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[12]	24 ^[13]		
Units: Centimeters (cm)				
arithmetic mean (standard deviation)				
Baseline (n=9, 24)	89.1 (± 4.3)	102.3 (± 6.4)		
Absolute Change in Week 12 (n=9, 23)	4.6 (± 1.2)	5.4 (± 1.1)		
Absolute Change in Week 24 (n=9, 23)	6 (± 1.7)	7.7 (± 3.3)		
Absolute Change in Week 36 (n=9, 23)	7.8 (± 1.8)	8.8 (± 1.4)		
Absolute Change in Week 48 (n=9, 21)	9.7 (± 2)	10.4 (± 1.7)		
Absolute Change in Week 60 (n=9, 22)	11 (± 2.2)	11.6 (± 2)		
Absolute Change in Week 72 (n=9, 20)	12.5 (± 2.6)	13.4 (± 2)		
Absolute Change in Week 84 (n=9, 19)	13.6 (± 2.3)	15 (± 2.3)		

Notes:

[12] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[13] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Study 109 in Stature at Week 12, 24, 36, 48, 60, 72 and 84

End point title	Absolute Change From Baseline of Study 109 in Stature at Week 12, 24, 36, 48, 60, 72 and 84
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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. Baseline is defined as the most recent measurement prior to intake of the first dose of study drug in study 109 (2012-000386-20). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (study 109), Week 12, 24, 36, 48, 60, 72 and 84 (study 109)

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[14]	24 ^[15]		
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=9, 24)	91.7 (± 4.3)	105.8 (± 6.6)		
Absolute Change at Week 12 (n=9, 23)	2 (± 1.1)	1.8 (± 0.9)		
Absolute Change at Week 24 (n=9, 23)	3.4 (± 1.2)	4.1 (± 3.2)		
Absolute Change at Week 36 (n=9, 23)	5.2 (± 1.5)	5.2 (± 1.1)		
Absolute Change at Week 48 (n=9, 21)	7.2 (± 1.3)	6.8 (± 1.3)		
Absolute Change at Week 60 (n=9, 22)	8.4 (± 1.4)	8 (± 1.5)		
Absolute Change at Week 72 (n=9, 20)	10 (± 2.1)	9.8 (± 1.6)		
Absolute Change at Week 84 (n=9, 19)	11.1 (± 1.7)	11.4 (± 1.9)		

Notes:

[14] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[15] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Parent Study in Body Mass Index (BMI) at Week 12, 24, 36, 48, 60, 72 and 84

End point title	Absolute Change From Baseline of Parent Study in Body Mass Index (BMI) at Week 12, 24, 36, 48, 60, 72 and 84
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End point description:

BMI = (Weight [in kg]) divided by (Stature [in meters])². Baseline was defined as the most recent measurement prior to intake of the first dose of study drug in study 108 Part B (2012-000204-15). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (study 108), Week 12, 24, 36, 48, 60, 72 and 84 (study 109)

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[16]	24 ^[17]		
Units: Kilogram per square meter (kg/m ²)				
arithmetic mean (standard deviation)				
Baseline (n=9, 24)	15.74 (± 0.69)	16.06 (± 1.15)		
Absolute Change at Week 12 (n=9, 23)	0.03 (± 0.4)	0.09 (± 0.6)		
Absolute Change at Week 24 (n=9, 23)	0.31 (± 0.57)	-0.12 (± 0.9)		
Absolute Change at Week 36 (n=9, 23)	0.15 (± 0.52)	0.09 (± 0.73)		

Absolute Change at Week 48 (n=9, 22)	-0.31 (± 0.6)	-0.13 (± 0.77)		
Absolute Change at Week 60 (n=9, 22)	-0.12 (± 0.7)	-0.06 (± 0.9)		
Absolute Change at Week 72 (n=9, 20)	-0.38 (± 0.68)	0.09 (± 0.97)		
Absolute Change at Week 84 (n=9, 19)	-0.16 (± 0.96)	0.28 (± 0.97)		

Notes:

[16] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[17] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline of Study 109 in Body Mass Index (BMI) at Week 12, 24, 36, 48, 60, 72 and 84

End point title	Absolute Change From Baseline of Study 109 in Body Mass Index (BMI) at Week 12, 24, 36, 48, 60, 72 and 84
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End point description:

BMI = (Weight [in kg]) divided by (Stature [in meters]) ^2. Baseline is defined as the most recent measurement prior to intake of the first dose of study drug in study 109 (2012-000386-20). Safety set included all subjects who received at least 1 dose of study drug in study 109 (2012-000386-20). Here "n" signifies those subjects who were evaluable at the specified time points for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (study 109), Week 12, 24, 36, 48, 60, 72 and 84 (study 109)

End point values	Ivacaftor 50 mg	Ivacaftor 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[18]	24 ^[19]		
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline (n= 9, 24)	16.07 (± 0.55)	16.33 (± 1.12)		
Absolute Change at Week 12 (n= 9, 23)	-0.3 (± 0.6)	-0.16 (± 0.48)		
Absolute Change at Week 24 (n= 9, 23)	-0.02 (± 0.7)	-0.36 (± 1.03)		
Absolute Change at Week 36 (n= 9, 23)	-0.18 (± 0.83)	-0.16 (± 0.63)		
Absolute Change at Week 48 (n= 9, 22)	-0.64 (± 0.81)	-0.35 (± 0.57)		
Absolute Change at Week 60 (n= 9, 22)	-0.45 (± 0.82)	-0.29 (± 0.72)		
Absolute Change at Week 72 (n= 9, 20)	-0.71 (± 0.9)	-0.21 (± 0.78)		
Absolute Change at Week 84 (n= 9, 19)	-0.49 (± 1.09)	-0.01 (± 0.87)		

Notes:

[18] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

[19] - Subjects were to be analyzed based on their dosing as per parent study VX11-770-108 (2012-000204-15)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 97 (for subjects who completed study drug dosing); Day 1 up to 24 weeks after the last dose (up to Week 108, for subjects who prematurely discontinued study drug dosing)

Adverse event reporting additional description:

As per the planned analysis for this study, subjects were to be reported based on their dosing groups as per parent study VX11-770-108 (2012-000204-15).

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	Ivacaftor 50 mg
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Reporting group description:

Subjects who received ivacaftor 50 mg q12h in parent study VX11-770-108 (2012-000204-15), received either ivacaftor 50 mg q12h for subjects aged 2 to <6 years and weighing <14 kg or ivacaftor 75 mg q12h for subjects aged 2 to <6 years and ≥14 kg or ivacaftor 150 mg q12h for subjects ≥6 years in this study (2012-000386-20).

Reporting group title	Ivacaftor 75 mg
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Reporting group description:

Subjects who received ivacaftor 75 mg q12h in parent study VX11-770-108 (2012-000204-15), received either ivacaftor 50 mg q12h for subjects aged 2 to <6 years and weighing <14 kg or ivacaftor 75 mg q12h for subjects aged 2 to <6 years and ≥14 kg or ivacaftor 150 mg q12h for subjects ≥6 years in this study (2012-000386-20).

Serious adverse events	Ivacaftor 50 mg	Ivacaftor 75 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 9 (66.67%)	5 / 24 (20.83%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus test positive			

subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure anoxic			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	3 / 9 (33.33%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ivacaftor 50 mg	Ivacaftor 75 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	24 / 24 (100.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 9 (77.78%)	6 / 24 (25.00%)	
occurrences (all)	12	10	
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 9 (88.89%)	16 / 24 (66.67%)	
occurrences (all)	25	45	
Nasal congestion			
subjects affected / exposed	4 / 9 (44.44%)	3 / 24 (12.50%)	
occurrences (all)	6	3	
Rhinorrhoea			
subjects affected / exposed	4 / 9 (44.44%)	2 / 24 (8.33%)	
occurrences (all)	4	3	
Productive cough			
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Asthma			

subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Allergic sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Respiratory tract congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiration abnormal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Snoring			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Upper respiratory tract congestion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Encopresis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Onychophagia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Investigations			

Alanine aminotransferase increased		
subjects affected / exposed	1 / 9 (11.11%)	4 / 24 (16.67%)
occurrences (all)	1	4
Haemophilus test positive		
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	5
Aspartate aminotransferase increased		
subjects affected / exposed	1 / 9 (11.11%)	3 / 24 (12.50%)
occurrences (all)	1	3
Bacterial test positive		
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)
occurrences (all)	2	1
Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)
occurrences (all)	1	1
Pseudomonas test positive		
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)
occurrences (all)	2	0
Respiratory rate increased		
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)
occurrences (all)	1	1
Adenovirus test positive		
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)
occurrences (all)	1	0
Antibiotic resistant Staphylococcus test positive		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Blood alkaline phosphatase increased		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Influenza A virus test positive		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Lymph node palpable		

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Respiratory syncytial virus test positive subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	
Staphylococcus test positive subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	
Injury, poisoning and procedural complications Laceration subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 24 (4.17%) 1	
Arthropod bite subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Contusion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Eye injury subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Congenital, familial and genetic disorders Phimosis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Nervous system disorders Convulsion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	

Lethargy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	
Migraine subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 24 (4.17%) 1	
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3	0 / 24 (0.00%) 0	
Amblyopia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Cataract cortical subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Eye pruritus subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Lacrimation increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	6 / 9 (66.67%)	7 / 24 (29.17%)	
occurrences (all)	9	11	
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	5 / 24 (20.83%)	
occurrences (all)	0	6	
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)	
occurrences (all)	1	5	
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Tooth discolouration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 9 (33.33%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Dry skin			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Eczema subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Nail disorder subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Red man syndrome subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Micturition urgency subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 24 (4.17%) 1	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	4 / 24 (16.67%) 10	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	5 / 24 (20.83%) 10	
Sinusitis subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	3 / 24 (12.50%) 7	
Otitis media			

subjects affected / exposed	2 / 9 (22.22%)	4 / 24 (16.67%)
occurrences (all)	3	5
Upper respiratory tract infection		
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)
occurrences (all)	1	5
Gastroenteritis viral		
subjects affected / exposed	0 / 9 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	4
Pharyngitis streptococcal		
subjects affected / exposed	1 / 9 (11.11%)	3 / 24 (12.50%)
occurrences (all)	1	3
Nasopharyngitis		
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)
occurrences (all)	1	2
Rhinitis		
subjects affected / exposed	2 / 9 (22.22%)	1 / 24 (4.17%)
occurrences (all)	2	1
Bronchitis		
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)
occurrences (all)	1	1
Ear infection		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	2
Respiratory tract infection viral		
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	2
Varicella		
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	2
Gastroenteritis		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Hand-foot-and-mouth disease		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Herpangina		

subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Lower respiratory tract infection bacterial		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Lung infection pseudomonal		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Molluscum contagiosum		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Myringitis		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Parainfluenzae virus infection		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Pneumonia		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Rhinovirus infection		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Staphylococcal skin infection		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1
Streptococcal infection		
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)
occurrences (all)	1	0
Tonsillitis		
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	1

Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2014	Changes to frequency of selected safety laboratory tests, study visit windows, and safety laboratory test panel.
16 January 2015	Changes to frequency of selected safety and efficacy laboratory tests, and changes to medical history data collection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported