ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: October 3, 2012

ClinicalTrials.gov ID: NCT00457821

Study Identification

Unique Protocol ID: VX06-770-101

Brief Title: Safety Study of Ivacaftor in Subjects With Cystic Fibrosis

Official Title: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study of VX-770 to Evaluate Safety, Pharmacokinetics, and Biomarkers of CFTR Activity in Cystic Fibrosis (CF) Subjects With Genotype G551D

Secondary IDs:

Study Status

Record Verification: October 2012

Overall Status: Completed

Study Start: May 2007

Primary Completion: August 2008 [Actual]

Study Completion: August 2008 [Actual]

Sponsor/Collaborators

Sponsor: Vertex Pharmaceuticals Incorporated

Responsible Party: Sponsor

Collaborators: Cystic Fibrosis Foundation Therapeutics

Oversight

FDA Regulated?: Yes

Applicable Trial?: Section 801 Clinical Trial? Yes

	Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 74,633 Serial Number: 0000 Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 03/26/2007 Board Name: IRB-01 WIRB Board Affiliation: Western Institutional Review Board Phone: 1-800-562-4789 Email: clientservices@wirb.com
Data Monitoring?:	Yes
Plan to Share IPD?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary: The purpose of this study was to evaluate the safety and tolerability of ivacaftor in patients with cystic fibrosis (CF) who were aged 18 years or older and have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Ivacaftor is a potent and selective CFTR potentiator of wild-type, G551D, F508del, and R117H forms of human CFTR protein. Potentiators are pharmacological agents that increase the chloride ion transport properties of the channel in the presence of cyclic AMP-dependent protein kinase A (PKA) activation.

Detailed Description: This was a double-blind, placebo-controlled, cross-over, multiple dose study of up to 28 days of dosing, in subjects with cystic fibrosis (CF) who have a G551D-CTFR gene mutation. Enrollment of 39 subjects occurred at 15 centers in the US, Canada, and Germany.

The study was conducted in 2 parts:

- Part 1 consisted of Group A and Group B. Subjects in Group A (10 subjects) were randomized to receive 25 mg of ivacaftor every 12 hours [q12h] (4 subjects), 75 mg of ivacaftor q12h (4 subjects), or placebo (2 subjects) for 14 days. Following a 7- to 28-day washout period, subjects who received active study drug crossed over to the alternate dose strength of ivacaftor for an additional 14 days. Placebo subjects continued to receive placebo for an additional 14 days. Subjects in Group B (10 subjects) were randomized to receive 75 mg of ivacaftor q12h (4 subjects), 150 mg of ivacaftor q12h (4 subjects), or placebo (2 subjects) for 14 days. Following a 7- to 28-day washout period, the subjects who received active study drug crossed over to the alternate dose strength of ivacaftor for an additional 14 days. Placebo subjects continued to receive placebo for an additional 14 days.
- Part 2 consisted of Group C; these subjects did not participate in Part 1. Subjects were randomized to receive 150 mg of ivacaftor q12h (7 subjects), 250 mg of ivacaftor q12h (7 subjects), or placebo (4 subjects) for a total of 28 days. Ivacaftor doses studied in Part 2 were selected following an interim pharmacokinetic/pharmacodynamic (PK/PD) and statistical

analyses of data from Part 1. The 2 doses selected for Part 2 were anticipated to enable better definition of the optimal therapeutic dose.

Conditions

Conditions: Cystic Fibrosis

Keywords: G551D mutation
Fibrosis
Pancreatic Diseases
Digestive System Diseases
Lung Diseases
Respiratory Tract Diseases
Genetic Diseases, Inborn
Infant, Newborn, Diseases
Pathologic Processes

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 2

Intervention Model: Crossover Assignment

Number of Arms: 4

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Allocation: Randomized

Endpoint Classification: Safety Study

Enrollment: 39 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Ivacaftor Group A Subjects in Part 1 who first received 25 mg or 75 mg of ivacaftor every 12 hours (q12h) for 14 days, then crossed over to receive the alternate dose for another 14 days.	Drug: Ivacaftor 25 mg/75 mg 25 mg or 75 mg q12h for a total of 28 days (Part 1) Other Names: • VX-770
Experimental: Ivacaftor Group B	Drug: Ivacaftor 75 mg/150 mg

Arms	Assigned Interventions
Subjects in Part 1 who first received 75 mg or 150 mg of ivacaftor q12h for 14 days then crossed over to receive the alternate dose for another 14 days.	75 mg or 150 mg q12h for a total of 28 days (Part 1) Other Names: • VX-770
Experimental: Ivacaftor Group C Subjects in Part 2 who received 150 mg or 250 mg of ivacaftor q12h for 28 days.	Drug: Ivacaftor 150 mg or 250 mg 150 mg or 250 mg of ivacaftor q12h for 28 days (Part 2) Other Names: • VX-770
Placebo Comparator: Placebo Subjects who received placebo in Part 1 and subjects who received placebo in Part 2.	Drug: Placebo Given q12h for 28 days each in Part 1 and Part 2 of the study

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Weighing at least 40 kg
- Confirmed diagnosis of cystic fibrosis (CF) and G551D mutation in at least 1 allele
- Forced expiratory volume in 1 second (FEV1) of at least 40% of predicted normal for age, gender, and height
- Willing to remain on stable medication regimen for the duration of study participation
- No significant clinical laboratory abnormalities, not pregnant, and willing to use at least 2 highly effective birth control methods during Part 1 and 1 highly effective birth control method during Part 2 of the study
- No clinically significant abnormalities that would have interfered with the study assessments, as judged by the investigator

Exclusion Criteria:

- History of any illness or condition that might confound the results of the study or pose an additional risk in administering study drug to the subject
- Ongoing acute respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 14 days of Day 1 of the study
- History of alcohol, medication or illicit drug abuse within one year prior to Day 1
- Abnormal liver function ≥ 3x the upper limit of normal
- History of abnormal renal function (creatinine clearance < 50 mL/min using Cockcroft-Gault equation)

- History of solid organ or hematological transplantation
- Pregnant or breast-feeding (for women)
- Ongoing participation in another therapeutic clinical trial, or prior participation in an investigational drug study without appropriate washout
- Concomitant use of any inhibitors or inducers of cytochrome P450 3A4 (CYP3A4)

Contacts/Locations

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References

Citations: [Study Results] Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, Sagel SD, Hornick DB, Konstan MW, Donaldson SH, Moss RB, Pilewski JM, Rubenstein RC, Uluer AZ, Aitken ML, Freedman SD, Rose LM, Mayer-Hamblett N, Dong Q, Zha J, Stone AJ, Olson ER, Ordoñez CL, Campbell PW, Ashlock MA, Ramsey BW. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med. 2010 Nov 18;363(21):1991-2003. doi: 10.1056/NEJMoa0909825. PubMed 21083385

Links: URL: http://ghr.nlm.nih.gov/
Description Genetics Home Reference

URL: http://www.nlm.nih.gov/medlineplus/
Description Medline Plus

URL: http://www.clinicaltrials.gov/ct2/info/fdalinks
Description U.S. FDA Resources

Study Results

Participant Flow

Recruitment Details	Part 1 started on 10 May 2007 (signing of first informed consent). After obtaining consent, Part 1 screening evaluations were completed during Day -28 to Day -2. Part 2 started on 28 May 2008 (signing of first informed consent). Part 2 screening evaluations were also completed during Day -28 to Day -2 before the first dose of study drug.
Pre-Assignment Details	In Part 1, 21 subjects were randomized but 1 subject was excluded prior to dosing because the subject needed a protocol-prohibited medication. In Part 2, 20 subjects were randomized but 1 subject withdrew consent to the study prior to dosing.

Reporting Groups

	Description
Part 1: Placebo	Part 1: placebo every 12 hours (q12h); 14 days/14 days.
Part 1: 25 mg/75 mg	Part 1: Ivacaftor (25 mg/75 mg) every 12 hours (q12h); 14 days/14 days.
Part 1: 75 mg/25 mg	Part 1: Ivacaftor (75 mg/25 mg) every 12 hours (q12h); 14 days/14 days.
Part 1: 75 mg/150 mg	Part 1: Ivacaftor (75 mg/150 mg) every 12 hours (q12h); 14 days/14 days.
Part 1: 150 mg/75 mg	Part 1: Ivacaftor (150 mg/75 mg) every 12 hours (q12h); 14 days/14 days.
Part 2: 150 mg	Part 2: Ivacaftor (150 mg) q12h; 28 days
Part 2: 250 mg	Part 2: Ivacaftor (250 mg) q12h; 28 days
Part 2: Placebo	Part 2: placebo q12h; 28 days

Part 1

	Part 1: Placebo	Part 1: 25 mg/75 mg	Part 1: 75 mg/25 mg	Part 1: 75 mg/150 mg	Part 1: 150 mg/75 mg	Part 2: 150 mg
Started	4 [1]	4 [1]	5 [1]	4 [1]	4 [1]	0 [2]
Completed	4	4	4	4	4	0
Not Completed	0	0	1	0	0	0

[1] Number of subjects randomized
[2] Arm in Part 2 only

	Part 2: 250 mg	Part 2: Placebo
Started	0 [1]	0 [1]
Completed	0	0
Not Completed	0	0

[1] Arm in Part 2 only

Part 2

	Part 1: Placebo	Part 1: 25 mg/75 mg	Part 1: 75 mg/25 mg	Part 1: 75 mg/150 mg	Part 1: 150 mg/75 mg	Part 2: 150 mg
Started	0 [1]	0 [1]	0 [1]	0 [1]	0 [1]	8 [2]
Completed Study Drug Treatment	0	0	0	0	0	8
Completed	0	0	0	0	0	8
Not Completed	0	0	0	0	0	0
Withdrawal by Subject	0	0	0	0	0	0

[1] Arm in Part 1 only
[2] All subjects who received at least 1 dose of study drug (ivacaftor).

	Part 2: 250 mg	Part 2: Placebo
Started	7 [1]	5 [2]
Completed Study Drug Treatment	7 [3]	4
Completed	7	4
Not Completed	0	1
Withdrawal by Subject	0	1

[1] All subjects who received at least 1 dose of study drug (ivacaftor).
[2] All subjects who received at least 1 dose of study drug (placebo).
[3] 1 subject missed a 250-mg dose of ivacaftor on Day 28 of Part 2.

Baseline Characteristics

Reporting Groups

	Description
Part 1: Placebo	Part 1: placebo every 12 hours (q12h); 14 days/14 days.
Part 1: 25 mg/75 mg	Part 1: Ivacaftor (25 mg/75 mg) every 12 hours (q12h); 14 days/14 days.
Part 1: 75 mg/25 mg	Part 1: Ivacaftor (75 mg/25 mg) every 12 hours (q12h); 14 days/14 days.
Part 1: 75 mg/150 mg	Part 1: Ivacaftor (75 mg/150 mg) every 12 hours (q12h); 14 days/14 days.
Part 1: 150 mg/75 mg	Part 1: Ivacaftor (150 mg/75 mg) every 12 hours (q12h); 14 days/14 days.
Part 2: 150 mg	Part 2: Ivacaftor (150 mg) q12h; 28 days
Part 2: 250 mg	Part 2: Ivacaftor (250 mg) q12h; 28 days
Part 2: Placebo	Part 2: placebo q12h; 28 days

Baseline Measures

	Part 1: Placebo	Part 1: 25 mg/75 mg	Part 1: 75 mg/25 mg	Part 1: 75 mg/150 mg	Part 1: 150 mg/75 mg	Part 2: 150 mg
Overall Number of Participants	4	4	4	4	4	8

		Part 1: Placebo	Part 1: 25 mg/75 mg	Part 1: 75 mg/25 mg	Part 1: 75 mg/150 mg	Part 1: 150 mg/75 mg	Part 2: 150 mg
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
		34.5 (14.66)	33.5 (12.50)	38.5 (11.82)	26.3 (7.85)	23.5 (6.45)	25.6 (7.98)
Gender, Male/ Female Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
	Female	2 50%	3 75%	0 0%	3 75%	3 75%	5 62.5%
	Male	2 50%	1 25%	4 100%	1 25%	1 25%	3 37.5%
Race/Ethnicity, Customized Measure Type: Number Unit of measure: participants	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
Caucasian		4	4	4	4	4	8
Weight Mean (Standard Deviation) Unit of measure: kilograms	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
		70.05 (16.507)	66.05 (12.628)	73.43 (14.366)	57.48 (8.663)	59.35 (18.401)	61.19 (9.857)
Body Mass Index Mean (Standard Deviation) Unit of measure: kilograms per square meter	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
		24.195 (3.2002)	22.455 (2.3133)	23.653 (3.6216)	20.960 (2.2522)	20.788 (4.1527)	21.896 (0.9770)

		Part 1: Placebo	Part 1: 25 mg/75 mg	Part 1: 75 mg/25 mg	Part 1: 75 mg/150 mg	Part 1: 150 mg/75 mg	Part 2: 150 mg
Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) [1] Mean (Standard Deviation) Unit of measure: percentage of volume in liters	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
		64.902 (22.6821)	71.073 (27.2307)	54.885 (9.6772)	68.284 (24.7014)	49.270 (7.5615)	70.443 (25.4442)
		[1] Measure Description: Percent predicted for age, gender, and height.					
Genotype Measure Type: Number Unit of measure: participants	Number Analyzed	4 participants	4 participants	4 participants	4 participants	4 participants	8 participants
G551D/1078 DEL T		1	0	0	0	0	0
G551D/DELTA F508		3	4	4	2	3	7
G551D/G551D		0	0	0	0	1	0
G551D/N1303K		0	0	0	1	0	0
G551D/R553X		0	0	0	1	0	0
G551D/3849 AND 10KBC		0	0	0	0	0	0
G551D/6214 + 1G > 7T		0	0	0	0	0	1
G551D/G542X		0	0	0	0	0	0

	Part 2: 250 mg	Part 2: Placebo	Total
Overall Number of Participants	7	4	39

		Part 2: 250 mg	Part 2: Placebo	Total
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	7 participants	4 participants	39 participants
		26.0 (7.07)	26.8 (10.69)	28.7 (10.03)
Gender, Male/ Female Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	7 participants	4 participants	39 participants
	Female	3 42.86%	1 25%	20 51.28%
	Male	4 57.14%	3 75%	19 48.72%
Race/Ethnicity, Customized Measure Type: Number Unit of measure: participants	Number Analyzed	7 participants	4 participants	39 participants
Caucasian		7	4	39
Weight Mean (Standard Deviation) Unit of measure: kilograms	Number Analyzed	7 participants	4 participants	39 participants
		64.46 (13.027)	63.50 (7.391)	64.1 (12.42)
Body Mass Index Mean (Standard Deviation) Unit of measure: kilograms per square meter	Number Analyzed	7 participants	4 participants	39 participants
		22.703 (1.3980)	22.035 (0.6999)	22.3 (2.37)

		Part 2: 250 mg	Part 2: Placebo	Total
Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) [1] Mean (Standard Deviation) Unit of measure: percentage of volume in liters	Number Analyzed	7 participants	4 participants	39 participants
		72.674 (21.5223)	79.351 (28.7018)	67.3 (22.17)
		[1] Measure Description: Percent predicted for age, gender, and height.		
Genotype Measure Type: Number Unit of measure: participants	Number Analyzed	7 participants	4 participants	39 participants
G551D/1078 DEL T		0	0	1
G551D/DELTA F508		5	4	32
G551D/G551D		0	0	1
G551D/N1303K		0	0	1
G551D/R553X		0	0	1
G551D/3849 AND 10KBC		1	0	1
G551D/6214 + 1G > 7T		0	0	1
G551D/G542X		1	0	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Subjects With Adverse Events (Combined Part 1 and Part 2)
Measure Description	Adverse event data were collected up to the follow-up visit (5 to 9 days after last dose of study drug). Serious adverse events that were ongoing at the follow-up visit were followed until the event resolved, returned to baseline, or was determined to be a stable or chronic condition.

Time Frame	Baseline to Follow-up
Safety Issue?	Yes

Analysis Population Description

All randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).

Reporting Groups

	Description
Placebo	All subjects given placebo in Part 1 (n=4) and Part 2 (n=4)
Ivacaftor	All subjects given Ivacaftor in Part 1 (n=16) and Part 2 (n=15)

Measured Values

	Placebo	Ivacaftor
Number of Participants Analyzed	8	31
Number of Subjects With Adverse Events (Combined Part 1 and Part 2) Measure Type: Number Unit of measure: participants		
Subjects with AEs	7	26
Subjects with Related or Possibly Related AEs	3	13
Subjects with SAEs	0	1
Subjects with Related or Possibly Related SAEs	0	0

2. Primary Outcome Measure:

Measure Title	Number of Adverse Events (Combined Part 1 and Part 2)
Measure Description	Adverse event data were collected up to the follow-up visit (5 to 9 days after last dose of study drug). Serious adverse events that were ongoing at the follow-up visit were followed until the event resolved, returned to baseline, or was determined to be a stable or chronic condition.
Time Frame	Baseline to Follow-up
Safety Issue?	Yes

Analysis Population Description

All randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).

Reporting Groups

	Description
Placebo	All subjects given placebo in Part 1 (n=4) and Part 2 (n=4)
Ivacaftor	All subjects given Ivacaftor in Part 1 (n=16) and Part 2 (n=15)

Measured Values

	Placebo	Ivacaftor
Number of Participants Analyzed	8	31
Number of Adverse Events (Combined Part 1 and Part 2) Measure Type: Number Unit of measure: events		
Number of Adverse Events (AEs)	32	179
Number of Related or Possibly Related AEs	11	40
Number of Serious Adverse Events (SAEs)	0	2
Number of Related or Possibly Related SAEs	0	0

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Nasal Potential Difference (Combined Part 1 and Part 2)
Measure Description	The transepithelial nasal potential difference (NPD) is a direct measure of transepithelial ion transport. NPD under conditions of zero chloride concentration perfusion solution in the presence of isoproterenol was of primary interest.
Time Frame	14 days and 28 days
Safety Issue?	No

Analysis Population Description

Due to the crossover design in Part 1, subjects were counted once for each period; therefore, the 4 unique subjects who received placebo were counted as 8 subjects in the analyses for Part 1.

Reporting Groups

	Description
Placebo	All subjects given placebo every 12 hours (q12h) in Part 1 (n=4) and Part 2 (n=4)
25 mg Ivacaftor q12h	All subjects given the 25 mg dose q12h in Group A in Part 1 (n=4 x 2).

	Description
75 mg Ivacaftor q12h	All subjects given the 75 mg dose q12h in Group A (n=4 x 2) and Group B (n=4 x 2) in Part 1.
150 mg Ivacaftor q12h	All subjects given the 150 mg dose q12h in Group B in Part 1 (n=4 x 2) and Group C in Part 2 (n=8).
250 mg Ivacaftor q12h	All subjects given the 250 mg dose q12h in Group C (n=7) in Part 2.

Measured Values

	Placebo	25 mg Ivacaftor q12h	75 mg Ivacaftor q12h	150 mg Ivacaftor q12h	250 mg Ivacaftor q12h
Number of Participants Analyzed	12	7	15	16	7
Change From Baseline in Nasal Potential Difference (Combined Part 1 and Part 2) Least Squares Mean (95% Confidence Interval) Unit of measure: millivolts					
Zero Chloride + Isoproterenol, Day 14	-0.3 (-3.5 to 2.9)	-1.4 (-5.2 to 2.4)	-4.4 (-7.0 to -1.8)	-4.6 (-7.2 to -2.0)	-7.6 (-11.7 to -3.5)
Zero Chloride + Isoproterenol, Day ≥ 14	-0.5 (-4.1 to 3.1)	-1.3 (-5.2 to 2.6)	-4.5 (-7.3 to -1.7)	-5.3 (-7.9 to -2.6)	-8.4 (-12.3 to -4.5)
Amiloride, Day 14	0.3 (-5.2 to 5.9)	-0.1 (-6.1 to 5.8)	-4.2 (-8.3 to 0.0)	-9.9 (-14.2 to -5.6)	-5.5 (-12.2 to 1.1)
Amiloride, Day ≥ 14	-0.7 (-5.5 to 4.1)	-0.3 (-6.8 to 6.2)	-3.7 (-8.4 to -1.0)	-8.8 (-12.8 to -4.8)	-4.0 (-9.2 to 1.2)

Statistical Analysis 1 for Change From Baseline in Nasal Potential Difference (Combined Part 1 and Part 2)

Statistical Analysis Overview	Comparison Groups	Placebo, 25 mg Ivacaftor q12h, 75 mg Ivacaftor q12h, 150 mg Ivacaftor q12h, 250 mg Ivacaftor q12h
	Comments	Within-dose group and between-dose group analyses were performed, using a linear mixed effect model with baseline, dose, and period as fixed effects and subject as a random effect.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.05
	Comments	There was no adjustment for multiple comparisons.
	Method	Mixed Models Analysis
	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second [FEV1] (Combined Part 1 and Part 2)
Measure Description	Spirometry is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies. Relative change reflects the percent change from the baseline values [100% * (X-Y)/Y], where X and Y are post-baseline and baseline values, respectively.
Time Frame	14 days and 28 days
Safety Issue?	No

Analysis Population Description

Due to the crossover design in Part 1, subjects were counted once for each period; therefore, the 4 unique subjects who received placebo were counted as 8 subjects in the analyses for Part 1.

Reporting Groups

	Description
Placebo	All subjects given placebo every 12 hours (q12h) in Part 1 (n=4) and Part 2 (n=4)
25 mg Ivacaftor q12h	All subjects given the 25 mg dose q12h in Group A in Part 1 (n=4 x 2).
75 mg Ivacaftor q12h	All subjects given the 75 mg dose q12h in Group A (n=4 x 2) and Group B (n=4 x 2) in Part 1.
150 mg Ivacaftor q12h	All subjects given the 150 mg dose q12h in Group B in Part 1 (n=4 x 2) and Group C in Part 2 (n=8).
250 mg Ivacaftor q12h	All subjects given the 250 mg dose q12h in Group C (n=7) in Part 2.

Measured Values

	Placebo	25 mg Ivacaftor q12h	75 mg Ivacaftor q12h	150 mg Ivacaftor q12h	250 mg Ivacaftor q12h
Number of Participants Analyzed	10	7	15	16	7

	Placebo	25 mg Ivacaftor q12h	75 mg Ivacaftor q12h	150 mg Ivacaftor q12h	250 mg Ivacaftor q12h
Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second [FEV1] (Combined Part 1 and Part 2) Least Squares Mean (95% Confidence Interval) Unit of measure: percent predicted (%)					
Absolute Change from Baseline, Day 14	0.5 (-3.4 to 4.5)	2.7 (-1.8 to 7.1)	5.1 (2.0 to 8.3)	6.9 (3.9 to 10.0)	8.4 (3.7 to 13.2)
Absolute Change from Baseline, Day ≥ 14	2.1 (-1.3 to 5.6)	2.5 (-1.3 to 6.2)	5.3 (2.4 to 8.1)	6.9 (4.4 to 9.5)	6.7 (3.1 to 10.3)
Relative Change from Baseline, Day 14	2.0 (-4.8 to 8.9)	4.7 (-2.7 to 12.2)	9.5 (4.1 to 14.8)	10.8 (5.6 to 15.9)	12.0 (3.8 to 20.1)
Relative Change from Baseline, Day ≥ 14	3.3 (-2.4 to 9.1)	4.1 (-1.9 to 10.1)	9.3 (4.7 to 13.9)	10.6 (6.5 to 14.8)	9.4 (3.4 to 15.4)

Statistical Analysis 1 for Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second [FEV1] (Combined Part 1 and Part 2)

Statistical Analysis Overview	Comparison Groups	Placebo, 25 mg Ivacaftor q12h, 75 mg Ivacaftor q12h, 150 mg Ivacaftor q12h, 250 mg Ivacaftor q12h
	Comments	Within-dose group and between-dose group analyses were performed, using a linear mixed effect model with baseline, dose, and period as fixed effects and subject as a random effect.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.05
	Comments	There was no adjustment for multiple comparisons.
	Method	Mixed Models Analysis
	Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score (Part 2 Only)(Respiratory Domain Score)

Measure Description	The CFQ-R is a health-related quality of life measure for subjects with cystic fibrosis. Each domain is scored from 0 (worst) to 100 (best). A difference of at least 4 points in the respiratory domain score of the CFQ-R is considered a minimal clinically important difference (MCID).
Time Frame	14 days and 28 days
Safety Issue?	No

Analysis Population Description

Part 2 is a parallel study. Subjects were counted only once for each treatment group.

Reporting Groups

	Description
Placebo	Subjects given placebo every 12 hours (q12h) for 28 days.
150 mg Ivacaftor q12h	Subjects given 150 mg of ivacaftor q12h for 28 days.
250 mg Ivacaftor q12h	Subjects given 250 mg of ivacaftor q12h for 28 days.

Measured Values

	Placebo	150 mg Ivacaftor q12h	250 mg Ivacaftor q12h
Number of Participants Analyzed	4	8	7
Change From Baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score (Part 2 Only) (Respiratory Domain Score) Mean (Standard Deviation) Unit of measure: score on a scale			
Baseline Respiratory Domain Score	70.8 (21.5)	68.8 (23.9)	73.0 (8.7)
Change from Baseline in Respiratory Score, Day 14	2.8 (7.2)	6.3 (6.9)	5.6 (7.9)
Change from Baseline in Respiratory Score, Day 28	2.8 (7.2)	6.9 (6.5)	11.9 (14.1)

6. Secondary Outcome Measure:

Measure Title	Change From Baseline in Maximum Sweat Chloride Concentration (Combined Part 1 and Part 2)
Measure Description	The sweat chloride (quantitative pilocarpine iontophoresis) test is a standard diagnostic tool for cystic fibrosis (CF), serving as an indicator of cystic fibrosis transmembrane conductance regulator (CFTR) activity.
Time Frame	14 days and 28 days

Safety Issue?	No

Analysis Population Description

Due to the crossover design in Part 1, subjects were counted once for each period; therefore, the 4 unique subjects who received placebo were counted as 8 subjects in the analyses for Part 1.

Reporting Groups

	Description
Placebo	All subjects given placebo every 12 hours (q12h) in Part 1 (n=4) and Part 2 (n=4)
25 mg Ivacaftor q12h	All subjects given the 25 mg dose q12h in Group A in Part 1 (n=4 x 2).
75 mg Ivacaftor q12h	All subjects given the 75 mg dose q12h in Group A (n=4 x 2) and Group B (n=4 x 2) in Part 1.
150 mg Ivacaftor q12h	All subjects given the 150 mg dose q12h in Group B in Part 1 (n=4 x 2) and Group C in Part 2 (n=8).
250 mg Ivacaftor q12h	All subjects given the 250 mg dose q12h in Group C (n=7) in Part 2.

Measured Values

	Placebo	25 mg Ivacaftor q12h	75 mg Ivacaftor q12h	150 mg Ivacaftor q12h	250 mg Ivacaftor q12h
Number of Participants Analyzed	12	8	14	16	7
Change From Baseline in Maximum Sweat Chloride Concentration (Combined Part 1 and Part 2) Least Squares Mean (95% Confidence Interval) Unit of measure: millimoles per liter					
Change from Baseline in Sweat Chloride, Day 14	2.0 (-9.1 to 13.1)	-33.8 (-43.4 to -24.2)	-42.0 (-49.9 to -34.1)	-46.0 (-53.9 to -38.2)	-27.1 (-39.7 to -14.6)
Change from Baseline in Sweat Chloride, Day ≥14	4.9 (-5.3 to 15.0)	-32.9 (-41.7 to -24.2)	-40.8 (-48.1 to -33.5)	-44.2 (-51.1 to -37.3)	-28.2 (-39.0 to -17.4)

Statistical Analysis 1 for Change From Baseline in Maximum Sweat Chloride Concentration (Combined Part 1 and Part 2)

Statistical Analysis Overview	Comparison Groups	Placebo, 25 mg Ivacaftor q12h, 75 mg Ivacaftor q12h, 150 mg Ivacaftor q12h, 250 mg Ivacaftor q12h
	Comments	Within-dose group and between-dose group analyses were performed, using a linear mixed effect model with baseline, dose, and period as fixed effects and subject as a random effect.

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.05
	Comments	There was no adjustment for multiple comparisons.
	Method	Mixed Models Analysis
	Comments	[Not specified]

Reported Adverse Events

Time Frame	Adverse event data were collected up to the follow-up visit (5 to 9 days after last dose of study drug).
Additional Description	[Not specified]

Reporting Groups

	Description
Placebo	All subjects given placebo every 12 hours (q12h) in Part 1 (n=4) and Part 2 (n=4)
25 mg Ivacaftor q12h	All subjects given the 25 mg dose q12h in Group A in Part 1 (n=4 x 2).
75 mg Ivacaftor q12h	All subjects given the 75 mg dose q12h in Group A (n=4 x 2) and Group B (n=4 x 2) in Part 1.
150 mg Ivacaftor q12h	All subjects given the 150 mg dose q12h in Group B in Part 1 (n=4 x 2) and Group C in Part 2 (n=8).
250 mg Ivacaftor q12h	All subjects given the 250 mg dose q12h in Group C (n=7) in Part 2.

Serious Adverse Events

	Placebo		25 mg Ivacaftor q12h		75 mg Ivacaftor q12h		150 mg Ivacaftor q12h		250 mg Ivacaftor q12h	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	0/8 (0%)		0/8 (0%)		0/16 (0%)		1/16 (6.25%)		0/7 (0%)	

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo		25 mg Ivacaftor q12h		75 mg Ivacaftor q12h		150 mg Ivacaftor q12h		250 mg Ivacaftor q12h	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	7/8 (87.5%)		4/8 (50%)		13/16 (81.25%)		13/16 (81.25%)		6/7 (85.71%)	

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is more than 60 days but less than or equal to 180 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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