



## Ivacaftor in Subjects With Cystic Fibrosis Who Are Homozygous for the F508del-CFTR Mutation

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**Background:** Ivacaftor (VX-770) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator that was approved in the United States for the treatment of cystic fibrosis (CF) in patients  $\geq 6$  years of age who have a G551D mutation; however, the most prevalent disease-causing CFTR mutation, F508del, causes a different functional defect. The objectives of this study were to evaluate the safety of ivacaftor in a larger population and for a longer time period than tested previously and to assess the efficacy of ivacaftor in subjects with CF who are homozygous for F508del-CFTR.

**Methods:** This was a phase 2 study with a 16-week randomized (4:1), double-blind, placebo-controlled period (part A) and an open-label extension (part B) for subjects who met prespecified criteria.

**Results:** Part A: The safety profile of ivacaftor was comparable to that of the placebo. The overall adverse event frequency was similar in the ivacaftor (87.5%) and placebo (89.3%) groups through 16 weeks. The difference in the change of FEV<sub>1</sub> % predicted from baseline through week 16 (primary end point) between the ivacaftor and placebo groups was 1.7% ( $P = .15$ ). Sweat chloride, a biomarker of CFTR activity, showed a small reduction in the ivacaftor vs placebo groups of  $-2.9$  mmol/L ( $P = .04$ ) from baseline through week 16. Part B: No new safety signals were identified. The changes in FEV<sub>1</sub> or sweat chloride in part A were not sustained with ivacaftor treatment from week 16 to week 40.

**Conclusions:** These results expand the safety information for ivacaftor and support its continued evaluation. Lack of a clinical effect suggests that a CFTR potentiator alone is not an effective therapeutic approach for patients who have CF and are homozygous for F508del-CFTR.

**Trial registry:** ClinicalTrials.gov; No.: NCT00953706; URL: [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

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**Abbreviations:** ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; HBE = human bronchial epithelial; ULN = upper limit of normal

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The encoded protein, CFTR, is an epithelial chloride channel that maintains hydration of lung secretions by regulating water absorption.<sup>1</sup> Inadequate airway hydration results in obstruction of the airways with thick mucus, rendering the airways vulnerable to chronic infection and inflammation, leading to irreversible structural changes and respiratory failure.

CF-causing CFTR mutations cause either diminished or defective CFTR protein in the apical membrane, resulting in decreased chloride transport.<sup>2</sup>

The most prevalent disease-causing CFTR mutation is F508del (c.1521\_1523delCTT).<sup>3-5</sup> Approximately 90% of patients with CF in North America have F508del on at least one allele, and nearly one-half are homozygous.<sup>6</sup> The F508del-CFTR mutation causes improper protein folding, resulting in little or no CFTR protein reaching the cell surface.<sup>7,8</sup> Furthermore, any F508del-CFTR protein reaching the cell surface may also have a defect in the opening and closing of the channel, known as a gating defect.<sup>9</sup>

Compounds designed to increase CFTR channel opening, CFTR potentiators, can prevent the hyperabsorption of water across the epithelial surface.<sup>9</sup>

Ivacaftor is a CFTR potentiator shown to increase chloride transport by activated CFTR channels at the cell surface in vitro.<sup>10</sup> *G551D-CFTR* (c.1652G > A) is the most common gating mutation associated with CF disease, having an allelic frequency of only approximately 2.2%.<sup>11</sup> Ivacaftor was tested for up to 4 weeks in a small number of subjects with CF who had the *G551D-CFTR* mutation on at least one *CFTR* allele<sup>12</sup> and has been approved in the United States for the treatment of CF in patients who are  $\geq 6$  years of age and have a *G551D* mutation.

This study aimed to evaluate the safety profile of ivacaftor in a larger CF population (ie, subjects homozygous for the *F508del-CFTR* mutation). This patient population was chosen (1) because *F508del-CFTR* is the most common CF-causing mutation, and patients with *F508del* on both alleles account for about 50% of the population with CF; (2) to explore potential efficacy because in vitro studies have suggested that a small amount of *F508del-CFTR* may reach the cell surface in some patients with the *F508del* mutation, and tissues derived from these patients show a limited response to CFTR potentiation<sup>9,13,14</sup>; and (3) because *F508del-CFTR* may respond to ivacaftor in some subjects, and most subjects enrolled in the *G551D* study had *F508del* on the other *CFTR* allele, a study of ivacaftor in subjects homozygous for the *F508del-CFTR* mutation may help isolate possible potentiation of *F508del* without a second mutation confounding the results.

## MATERIALS AND METHODS

### Study Design

This was a two-part, phase 2, multicenter, randomized (4:1), placebo-controlled, double-blind study of ivacaftor (Kalydeco,

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\*A complete list of study participants is located in e-Appendix 1.

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formerly known as VX-770; Vertex Pharmaceuticals Incorporated), 150 mg po administered every 12 h for 16 weeks (part A), followed by an open-label 96-week extension for subjects who met prespecified eligibility criteria (part B). The rationale for selecting subjects for the open-label extension was to determine whether the changes from baseline observed in part A of the study persisted. Prespecified eligibility criteria for enrollment in part B included either  $\geq 10\%$  change relative to baseline in FEV<sub>1</sub> % predicted at any time point through week 16, or a sweat chloride concentration reduction from baseline  $\geq 15$  mmol/L at both the day 15 and week 8 visits. Interim analyses were planned to occur every 6 months, the first of which was performed at week 40. The protocol was approved by each site's institutional review board, and subjects provided written informed consent and assent as applicable.

The study included clinically stable subjects aged  $\geq 12$  years with CF, homozygous for the *F508del-CFTR* mutation, with an FEV<sub>1</sub>  $\geq 40\%$  predicted at screening. Subjects remained on their prestudy stable medication regimens throughout the study, including cycling inhaled antibiotics. Use of inhaled hypertonic saline or known inhibitors or inducers of cytochrome P450 3A4 was not allowed.

### End Points

The primary end point of safety was evaluated by assessment of adverse events, clinical laboratory values, ECGs, vital signs, and physical examinations. ECG monitoring included standard 12-lead digital and 24-h ambulatory ECG (conducted at day 14 and week 16 visits); data were interpreted by a cardiologist at the Central ECG laboratory.

The primary efficacy end point was the absolute change in FEV<sub>1</sub> % predicted from baseline through week 16. Secondary efficacy end points were change from baseline through week 16 in sweat chloride concentration, change in weight, and patient-reported health using the disease-specific Cystic Fibrosis Questionnaire-Revised.<sup>15</sup> Spirometry was performed according to American Thoracic Society guidelines.<sup>16</sup> Sweat chloride collection was performed according to a standardized protocol using the Macroduct (Wescor, Inc) collection device<sup>17</sup> and was evaluated centrally.

Analyses of other clinically relevant events, including time to first pulmonary exacerbation, duration and frequency of exacerbations using a modified Fuchs definition,<sup>18</sup> hospitalizations, and use of antibiotics for sinopulmonary signs and symptoms, were prespecified tertiary end points. Investigator-reported pulmonary exacerbations were also captured as adverse events.

### Statistical Analyses

Because the primary end point was safety, no formal sample size calculations were performed. Based on clinical considerations, a sample size of 120 subjects was selected to provide additional safety data on ivacaftor in this population. With 96 subjects in the ivacaftor group, the 90% CI estimates for the true adverse event rate were 7.4% and 19.5% if 12 subjects should have an adverse event, 2.8% and 12% should six subjects have an adverse event, and 0.4% and 6.4% should two subjects have an adverse event. The analysis suggests that this sample size was adequate to evaluate the safety of this drug in this population.

Analyses were performed on all randomized subjects who received at least one dose of the study drug. Analyses for safety are presented using descriptive statistics only and were not subjected to hypothesis testing. Primary analyses for efficacy end points were based on mixed-effects models for repeated measures with adjustments for age and baseline FEV<sub>1</sub>. Analyses of individual subject responses based on FEV<sub>1</sub> and sweat chloride

were performed using the predetermined criteria for enrollment in part B and two additional criteria, for a threshold response predetermined in the statistical analysis plan (ie, a mean decrease in sweat chloride of  $\geq 10$  mmol/L and  $\geq 15$  mmol/L from baseline), and differences between groups were compared using the Pearson  $\chi^2$  test or Fisher exact test. Additional details on study methodology can be found in e-Appendix 2.

## RESULTS

### Subjects

The study was conducted between September 2009 and July 2010. Thirty-four study sites in the United States enrolled and randomized 140 subjects (ivacaftor,  $n = 112$ ; placebo,  $n = 28$ ). The groups were generally similar at baseline (Table 1).

A total of 104 subjects (92.9%) in the ivacaftor group and 26 (92.9%) in the placebo group completed dosing in part A (Fig 1). The most frequent reason for discontinuation was an adverse event (three subjects [2.7%] in the ivacaftor group and two subjects [7.1%] in the placebo group). Forty-two ivacaftor subjects (37.5%) and six placebo subjects (21.4%) qualified for part B; the difference was not statistically significant ( $P = .11$ ).

### Safety Profile

The overall proportion of subjects reporting any adverse event was similar between the groups, and the most common events were respiratory related (Table 2). Adverse events that occurred  $\geq 5\%$  more

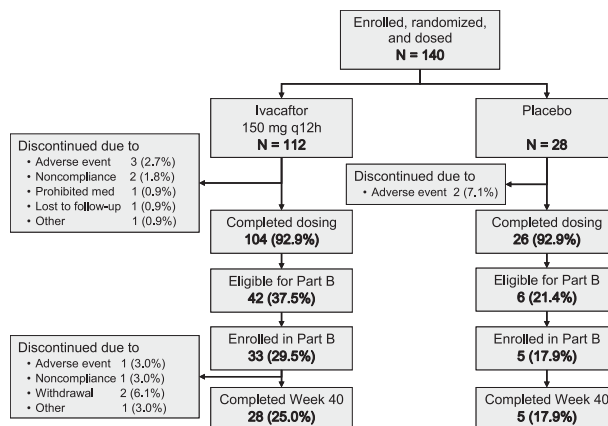


FIGURE 1. Subject flow diagram (following Consolidated Standards of Reporting Trials guidelines).

often in the ivacaftor group than in the placebo group were cough, nausea, rash, and contact dermatitis. None of these events was serious or led to study drug discontinuation. Conversely, investigator-identified pulmonary exacerbations occurred in a lower proportion of subjects treated with ivacaftor compared with placebo.

Adverse events were mostly mild (35%) or moderate (45%) in severity. One subject (0.9%) in the ivacaftor group had three adverse events considered life threatening: fatigue, depression, and suicidal ideation. Ten subjects (8.9%) in the ivacaftor group had 14 adverse events considered by the investigator to be severe; all were single events of nasal congestion, nasal polyps, epistaxis, increased viscosity of bronchial secretions, sinusitis, laryngitis, pulmonary exacerbation, diarrhea, dental caries, asthenia, rash, headache, arthritis, and nephrolithiasis. No severe events were reported in the placebo group. No deaths occurred during the study. Twenty-one subjects (15.0%) had at least one event that met the criteria for a serious adverse event, including 15 (13.4%) in the ivacaftor group and six (21.4%) in the placebo group. This difference was predominantly due to pulmonary exacerbations, which were more frequent in the placebo group ( $n = 5$ , 17.9%) than in the ivacaftor group ( $n = 10$ , 8.9%). Other serious adverse events were single events of hemoptysis, hypoxia, nasal polyps, abdominal pain, myopathy, fatigue, depression, and suicidal ideation in the ivacaftor group; and bronchopneumonia, cognitive disorder, and venous thrombosis in the placebo group.

In the ivacaftor group, three subjects (2.7%) were discontinued from the study because of a total of five events, which included asthenia, fatigue, and headache in one subject, arthritis in another, and myopathy in the third. In the placebo group, two subjects (7.1%) were discontinued because of adverse events of abnormal feelings and cognitive disorder in one subject,

**Table 1—Baseline Characteristics of Study Participants**

Characteristic	Placebo (n = 28)	Ivacaftor (n = 112)
Female, No. (%)	12 (43)	54 (48)
Age, y		
Mean (SD)	25.0 (8.4)	22.8 (10.3)
Median	24.0	19.5
Range	12-39	12-52
Height, cm		
Median	170.7	164.0
Range	145.6-184.0	139.0-189.6
Weight, kg		
Median	64.9	55.9
Range	44.2-100.3	35.1-99.8
BMI, kg/m <sup>2</sup>		
Median	21.5	20.4
Range	17.9-40.8	15.7-31.6
Sweat chloride, mmol/L		
Mean (SD)	102.4 (7.9)	101.4 (10.3)
Median	101.5	101.0
Range	91.0-122.0	79.5-135.5
FEV <sub>1</sub> % predicted		
Mean (SD)	74.8 (24.1)	79.7 (22.7)
Median	67.0	79.0
Range	43-127	40-129

None of the characteristics differed significantly between the groups ( $P > .05$  for all comparisons).

and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) elevated more than eight times the upper limit of normal (ULN) and increased lactate dehydrogenase levels in another subject. The liver enzyme abnormalities may have been due to concomitant use of an anabolic-steroid-like nutritional supplement. The liver enzyme elevations in the placebo subject were considered to be of moderate severity and resolved without treatment. The majority of subjects had ALT (90.7%), AST (94.3%), or total bilirubin (98.6%) values that remained less than or equal to two times ULN. Four subjects (3.6%) in the ivacaftor group and two (7.1%) in the placebo group had at least one measured ALT and/or AST value greater than three times ULN. Study drug dosing was interrupted for two of these ivacaftor subjects, but alternative causes of liver enzyme increases were identified in both cases (gallstones with focal nodular hyperplasia and use of acetaminophen with alcohol); in both cases, dosing was resumed and tolerated well for the remainder of the treatment period. There were no clinically important trends attributable to ivacaftor identified in clinical laboratory (serum chemistry, hematology, coagulation studies, and urinalysis), vital sign, digital ECG, ambulatory ECG, or physical examination results.

### Efficacy Measures

**Lung Function Results:** The adjusted mean absolute change from baseline through week 16 in FEV<sub>1</sub> % predicted in the ivacaftor group was an estimated treatment difference of 1.7% (95% CI, -0.6 to 4.1)

compared with placebo; however, this difference was not statistically significant ( $P = .15$ ). This corresponded to a relative change of 2.4% (95% CI, -0.9 to 5.8;  $P = .16$ ). No statistically significant differences were seen for other spirometric parameters (ie, FVC, forced expiratory flow at 25%-75% capacity). The number of subjects who qualified for the extension period on the basis of FEV<sub>1</sub> improvement was also not statistically significant ( $P = .46$ ) between ivacaftor (36 [32.1%]) and placebo (seven [25.0%]).

**Sweat Test Results:** The adjusted mean sweat chloride concentration decreased slightly from baseline through week 16 in the ivacaftor group, whereas there was no change in placebo, with an estimated treatment difference of -2.9 mmol/L (95% CI, -5.6 to -0.2); this difference was statistically significant ( $P = .04$ ). The change in sweat chloride occurred by day 15 and was sustained throughout the 16 weeks (Fig 2).

As described in the "Materials and Methods" section, (a priori) threshold changes in sweat chloride were established that would be used for analysis. A subset of ivacaftor subjects met one or more of these predetermined criteria for change in sweat chloride, whereas no placebo subjects met any of these criteria. Six subjects (5.4%,  $P = .6$ ) had a change in sweat chloride  $\geq 15$  mmol/L at both the day 15 and week 8 visits (the criterion for eligibility for part B), eight (7.1%,  $P = .36$ ) had a mean decrease of  $\geq 15$  mmol/L from baseline, and 17 (15.2%,  $P = .02$ ) had a mean decrease of  $\geq 10$  mmol/L from baseline averaged across all time points through week 16.

**Other Clinically Relevant Measures:** There were no significant differences in either the ivacaftor or placebo group in the Cystic Fibrosis Questionnaire-Revised respiratory domain scores, pulmonary exacerbations, or antibiotic treatment of sinopulmonary signs or symptoms (Table 3). Change from baseline in weight and BMI (all subjects) and weight-for-age and BMI-for-age  $z$  score (subjects  $\leq 20$  years; ivacaftor,  $n = 56$ ; placebo,  $n = 7$ ) were not significantly different between arms.

### Open-Label Extension Period (Part B)

Of 42 ivacaftor subjects in part A eligible for enrollment in part B, 33 entered the open-label period. Twenty-eight of these subjects met the FEV<sub>1</sub> criterion and five met the sweat chloride criterion. Of six placebo subjects eligible for part B, five subjects enrolled, all on the basis of FEV<sub>1</sub> changes.

There were no meaningful findings regarding safety, lung function, and sweat chloride with continued treatment with ivacaftor. Further details of the results in part B are included in e-Appendix 2.

**Table 2—Most Common Adverse Events Reported During the Study by Treatment Group**

Adverse Event	Placebo (n = 28)	Ivacaftor (n = 112)
Subjects with any adverse event	25 (89.3)	98 (87.5)
Cough	4 (14.3)	34 (30.4)
Pulmonary exacerbation <sup>a</sup>	11 (39.3)	25 (22.3)
Nasal congestion	2 (7.1)	13 (11.6)
Headache	2 (7.1)	11 (9.8)
Upper respiratory tract infection	2 (7.1)	11 (9.8)
Nausea	1 (3.6)	10 (8.9)
Oropharyngeal pain	3 (10.7)	10 (8.9)
Fatigue	3 (10.7)	9 (8.0)
Productive cough	1 (3.6)	9 (8.0)
Pyrexia	2 (7.1)	9 (8.0)
Rash	0	9 (8.0)
Sinusitis	1 (3.6)	8 (7.1)
Upper abdominal pain	1 (3.6)	7 (6.3)
Increase in C-reactive protein	1 (3.6)	6 (5.4)
Contact dermatitis	0	6 (5.4)
Diarrhea	2 (7.1)	6 (5.4)

Data are presented as No. (%). Minimum frequency of 5% of subjects in the ivacaftor group.

<sup>a</sup>Coded as cystic fibrosis lung.

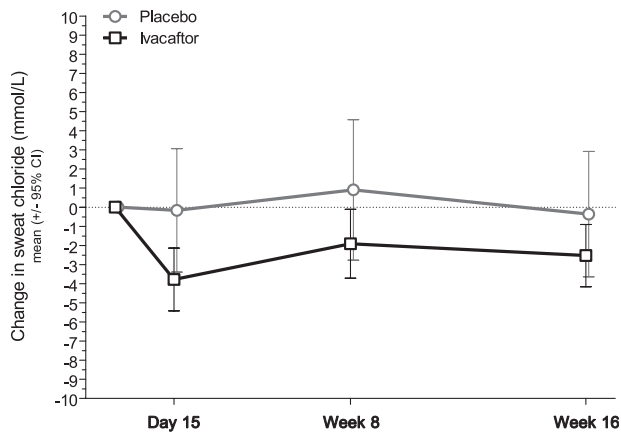


FIGURE 2. Average change from baseline ( $\pm$  95% CI) in sweat chloride concentration, a biomarker of cystic fibrosis transmembrane conductance regulator chloride transport activity. A greater proportion of subjects had a mean decrease from baseline through week 16 of  $\geq 10$  mmol/L (ivacaftor [15.2%] vs placebo [0];  $P = .0240$ ).

## DISCUSSION

This randomized, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of the CFTR potentiator, ivacaftor, in subjects with CF homozygous for the *F508del-CFTR* mutation. The safety profile of ivacaftor compared with placebo in this study supports further clinical evaluation in patients with CF. Treatment with ivacaftor was not associated with significant improvements in FEV<sub>1</sub> or other clinical end points. There was a small reduction in sweat chloride concentration observed during the randomized controlled portion of the study that was not reflected in the population enrolled in the open-label extension.

Gaining additional safety experience with ivacaftor was a primary study objective. The incidence of adverse events was generally similar between ivacaftor and placebo, with many of the most common events being respiratory related, as expected in patients with CF. Cough, rash, and contact dermatitis occurred more frequently in the ivacaftor group, whereas pulmonary

exacerbation as defined by the treating physician was reported more frequently in the placebo group. The numeric differences between arms may be due to the small sample size in the placebo group resulting from the skewed randomization. All adverse events considered severe by the investigator were reported in the ivacaftor group. One possible explanation for this finding is chance, given that more subjects were randomized to ivacaftor than to placebo (4:1 ratio); there would need to be only two subjects (about 7%) in the placebo group for there to be no difference. Conversely, there was a higher frequency of serious adverse events (eg, hospitalization) reported in the placebo group, supporting the conclusion that treatment with ivacaftor does not lead to clinically important safety concerns. No new safety events arose during the 40-week open-label extension.

Another objective of the study was to explore potential clinical improvement with ivacaftor treatment, although the study was powered based on safety, not efficacy. There were no statistically significant improvements in pulmonary function with ivacaftor treatment in *F508del-CFTR* homozygous subjects. Similarly, no notable changes were observed for other clinical end points, including weight gain and patient-reported respiratory symptoms. A numeric difference between treatment groups in the risk of pulmonary exacerbations over 16 weeks did not achieve statistical significance. It should be noted that some subjects in the placebo group met the criterion for Part B by experiencing an improvement in their FEV<sub>1</sub>. Such an increase in some subjects is not unusual in CF trials. Possible explanations include artificially low baseline and regression to mean, a change related to chronic therapies (eg, inhaled cycled antibiotics), or improvement due to antibiotic use during exacerbation.

Sweat chloride concentration, a measure of CFTR function, showed a small decrease (2.9 mmol/L) compared with placebo through 16 weeks of therapy, although this change was not sustained for the majority of subjects in the open-label extension period. By contrast, ivacaftor demonstrated a median change

Table 3—Other Clinically Relevant Measures

Measure	Placebo (n = 28)	Ivacaftor (n = 112)
Absolute change in FEV <sub>1</sub> % predicted	-0.2	1.5
Absolute change in CFQ-R respiratory domain score	-1.4	-0.1
Absolute change in weight, kg	0.96	0.84
Absolute change in BMI, kg/m <sup>2</sup>	0.25	0.21
Absolute change in weight-for-age z score	0.0007	0.43
Absolute change in BMI-for-age z score	-0.002	0.73
Pulmonary exacerbation, <sup>a</sup> No. (%)	10 (32)	25 (21)
Antibiotic treatment of sinopulmonary signs or symptoms, <sup>b</sup> No. (%)	16 (56)	48 (43)

*P* values for all measures were not significant. CFQ-R = Cystic Fibrosis Questionnaire-Revised.

<sup>a</sup>Treatment with new or changed antibiotic therapy for  $\geq 4$  sinopulmonary signs/symptoms.

<sup>b</sup>Events requiring new or changed antibiotic therapy for  $\geq 1$  sinopulmonary sign/symptom.

of  $-59.5$  mmol/L after 28 days at the same dose in the *G551D-CFTR* population.<sup>12</sup> Moreover, the *G551D-CFTR* trial also showed a significant improvement in FEV<sub>1</sub>. Interestingly, in the current study of *F508del-CFTR* homozygotes, 15.2% of ivacaftor subjects demonstrated an average sweat chloride reduction of  $\geq 10$  mmol/L across all time points through week 16, compared with no subjects in the placebo group. This may indicate a subpopulation of subjects homozygous for the *F508del-CFTR* mutation with some *F508del-CFTR* protein that reaches the epithelial cell surface, supporting *in vitro* evidence. One *in vitro* study tested ivacaftor in human bronchial epithelial (HBE) cells from subjects with CF who were homozygous for the *F508del-CFTR* mutation.<sup>10</sup> Among HBE that showed potentiation by ivacaftor, the effect size (up to 16% of normal activity) was considerably lower than in HBE from a *G551D/F508del* donor (nearly 50% normal).

## CONCLUSIONS

This study augments the safety information for ivacaftor and supports the continued evaluation of ivacaftor in subjects with CF. The lack of an observed clinical effect suggests that CFTR potentiation with ivacaftor alone will not benefit patients with CF who are homozygous for the *F508del-CFTR* mutation. Although a proportion of subjects treated with ivacaftor showed a small change in the sweat chloride biomarker, this was not associated with clinical benefit. Additional studies are needed to explore any relationship between sweat chloride and a clinical response in this group. Alternative therapeutic approaches, possibly using a corrector compound to increase the amount of *F508del-CFTR* protein that reaches the epithelial cell surface, should be evaluated for clinical benefit in this population.

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**Author contributions:** Dr Flume served as guarantor of the manuscript.

*Dr Flume:* contributed to the acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final version.

*Dr Liou:* contributed to the acquisition of data and critical revision of the manuscript for important intellectual content and saw and approved the final version.

*Dr Borowitz:* contributed to the acquisition of data and critical revision of the manuscript for important intellectual content and saw and approved the final version.

*Dr Li:* contributed to the analysis and interpretation of the data, statistical analysis and critical revision of the manuscript for important intellectual content and saw and approved the final version.

*Dr Yen:* contributed to the concept and design of the study, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content and saw and approved the final version.

*Dr Ordoñez:* contributed to the concept and design of the study, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content and saw and approved the final version.

*Dr Geller:* contributed to the acquisition of data and critical revision of the manuscript for important intellectual content and saw and approved the final version.

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**Additional information:** The e-Appendix can be found in the "Supplemental Materials" area of the online article.

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