



Long-Term Ivacaftor in People Aged 6 Years and Older with Cystic Fibrosis with Ivacaftor-Responsive Mutations

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ABSTRACT

Introduction: Mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) affect the quantity and/or function of

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CFTR protein reaching the cell surface. Ivacaftor, a *CFTR* potentiator that enhances chloride transport, increases the channel-open probability of normal and dysfunctional *CFTR*. Initially approved for people with CF (pwCF) with *G551D-CFTR* gating mutations, ivacaftor demonstrated clinical benefit in pwCF with other gating mutations and certain residual function mutations, including *R117H-CFTR*, in clinical studies. We evaluated the long-term safety and efficacy of ivacaftor in pwCF aged 6 years and older with non-*G551D-CFTR* ivacaftor-responsive mutations.

Methods: Efficacy and safety data from a phase 3, multicenter, open-label, extension study for participants from Study 110 (*R117H-CFTR* mutations), Study 111 (non-*G551D-CFTR* gating mutations), and Study 113 (*n-of-1* pilot study in participants with residual *CFTR* function) were analyzed. Following washout from the randomized parent study, participants received oral ivacaftor 150 mg once every 12 h for 104 weeks.

Results: Forty-one of 121 participants completed treatment through 104 weeks; 59 participants who did not complete the extension study continued treatment with commercial ivacaftor. The most common adverse events were pulmonary exacerbation (46.3%) and cough (33.9%). Most treatment-emergent adverse events were mild/moderate in severity and consistent with manifestations of CF or the ivacaftor safety profile. Rapid, durable

improvement occurred across all efficacy endpoints.

Conclusions: Ivacaftor was generally safe and well tolerated with no new safety concerns for up to 104 weeks in pwCF with ivacaftor-responsive mutations. The pattern of improvement across efficacy endpoints was durable and generally consistent with parent-study outcomes.

Trial Registration: NCT01707290

Keywords: Ivacaftor; Long-term efficacy; Long-term safety; Non-*G551D* mutation; Residual function; *R117H*; Gating mutation

Key Summary Points

Why carry out this study?

Initially approved for people with *G551D-CFTR* gating mutations, ivacaftor demonstrated clinical benefit in pwCF with other gating mutations and certain residual function mutations, including *R117H-CFTR*, in clinical studies.

We evaluated the long-term safety and efficacy of ivacaftor in pwCF aged ≥ 6 years with non-*G551D-CFTR* ivacaftor-responsive mutations in a rollover extension of three parent studies.

What was learned from the study?

Ivacaftor was generally safe and well tolerated with no new safety concerns for up to 104 weeks in pwCF with non-*G551D-CFTR* ivacaftor-responsive mutations.

The pattern of improvement across efficacy endpoints was durable and generally consistent with parent study outcomes.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*)

that affect the quantity and/or function of CFTR protein at the cell surface [1].

Ivacaftor (Kalydeco[®]) is a CFTR potentiator that enhances chloride transport by increasing the channel-open (i.e., gating) probability of both wild-type and dysfunctional CFTR protein at the cell surface [2]. Ivacaftor was initially approved in 2012 for the treatment of people with CF (pwCF) with a *G551D-CFTR* gating mutation [1, 2]. Since then, ivacaftor has demonstrated clinical benefit in more trials and in real-world data, and it is now approved in the United States for pwCF aged 6 months and older who have a mutation responsive to ivacaftor, including gating mutations and certain mutations associated with residual CFTR function (Appendix S1 in the supplement) [2–11]; currently approved genotypes and ages vary by country and region [2, 12]. Ivacaftor-responsive mutations have demonstrated responsiveness to ivacaftor in vitro and/or in clinical data [1, 2, 13].

This rollover extension study (Extension Study 112) was open to qualifying pwCF who had participated in one of three previous studies investigating the treatment effects of ivacaftor in CF: Study 110 (NCT01614457), in which participants had an *R117H-CFTR* mutation [8]; Study 111 (NCT01614470), in which participants had a non-*G551D-CFTR* gating mutation [6]; and Study 113, in which participants had phenotypic or molecular evidence of residual CFTR function (NCT01685801) [14].

The total duration of ivacaftor treatment in the three parent studies ranged from 12 to 24 weeks [6, 8, 14]. The primary objective of the present extension study was to evaluate the long-term safety of ivacaftor therapy in pwCF aged 6 years and older with ivacaftor-responsive mutations. The secondary objective was evaluation of long-term efficacy.

METHODS

Participants and Study Design

This was a phase 3, multicenter, open-label, extension study (NCT01707290) in pwCF who had previously enrolled in Study 110, Study

111, or Study 113 (Fig. 1). Participants received oral ivacaftor 150 mg once every 12 h for up to 104 weeks.

Participants entering from Study 110 or Study 111 must have completed their assigned study drug treatments in their respective parent studies. Participants entering from Study 113 must have completed study drug treatment through follow-up and met ≥ 1 of 4 responder criteria. For full responder criteria, see Appendix S2 in the supplement. Exclusion criteria included a history of any illness or condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering the study drug to the participant. For full inclusion and exclusion criteria, see Appendix S2 in the supplement.

This study was conducted in accordance with good clinical practices, as described in the International Council for Harmonisation guidelines, and is consistent with the World Medical Association Declaration of Helsinki and applicable regional laws and regulations. The study protocol, informed consent form, and other necessary documents were reviewed and approved by an independent ethics committee or institutional review board for each study site before initiation of the study at that site

(Table S1 in the supplement). Written informed consent was obtained from or for (with assent, where applicable) each participant on (or before) the day 1 visit.

Outcomes

The primary objective was to evaluate the long-term safety of ivacaftor treatment in pwCF aged 6 years and older with ivacaftor-responsive mutations. Safety outcomes included the incidence of treatment-emergent adverse events (AEs) and clinical laboratory measures. The secondary objective was to evaluate long-term efficacy. Secondary efficacy measures included mean absolute change from baseline in percent predicted forced expiratory volume in 1 s (ppFEV₁), sweat chloride concentration, respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R RD), measures of nutritional status, and time to first pulmonary exacerbation (PEX).

Statistical Methods

The full analysis set (FAS) was defined as all participants who received ≥ 1 dose of study drug during the extension study. All analyses

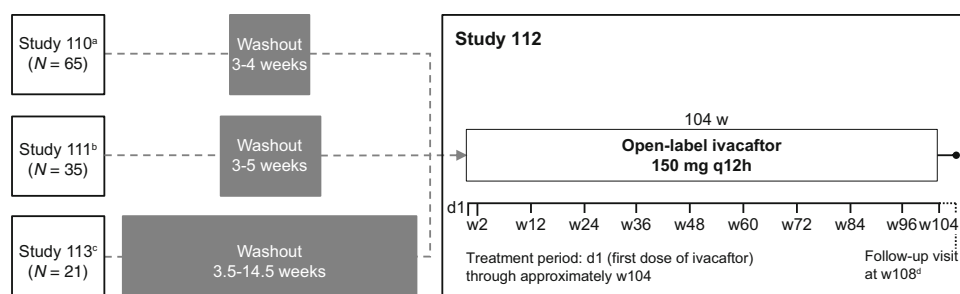


Fig. 1 Study design. ^aStudy 110 was a randomized controlled trial of ivacaftor vs. placebo for 24 weeks in pwCF who had an *R117H-CFTR* mutation; N is for the full analysis set. ^bStudy 111 was a randomized crossover trial of ivacaftor vs. placebo for 8 weeks per treatment, followed by 16 weeks of open-label ivacaftor, in pwCF who had a non-*G551D-CFTR* gating mutation; N is for the full analysis set. ^cStudy 113 was a randomized crossover trial of ivacaftor vs. placebo for a total of 4 weeks per treatment, followed by 8 weeks of open-label ivacaftor, in

pwCF who had phenotypic or molecular evidence of residual CFTR function; N is for the full analysis set. ^dFollow-up visit occurred 4 weeks (± 7 days) after the last ivacaftor dose for participants who did not continue immediately on ivacaftor. If applicable, an early termination visit occurred as soon as possible after the last ivacaftor dose. *CFTR* cystic fibrosis transmembrane conductance regulator, *d* day, *pwCF* people with cystic fibrosis, *q12h* once every 12 h, *w* week

were performed for the FAS and are presented by parent-study subgroup. No power or sample size analyses were conducted. Descriptive analyses of safety were performed.

For the secondary efficacy outcomes, mixed-effects models for repeated measures and least-squares (LS) means were used to assess absolute change from baseline in ppFEV₁, sweat chloride concentration, and CFQ-R RD score. For body mass index (BMI), a linear mixed-effects model was used to assess the change from baseline over 104 weeks, and the LS mean of the rate of change over 104 weeks was used. For analyses presenting change from baseline, the Extension Study 112 baseline following washout from the parent study, which was defined as the most recent nonmissing (scheduled or unscheduled) measurement collected before initial administration of the study drug in Extension Study 112, was used rather than that from the treatment period of the parent study. Kaplan–Meier methods were used to assess the time to first PEx by study day.

RESULTS

Of 121 participants who were enrolled and received ivacaftor in the extension study (Table 1; FAS shown in Figure S1 in the supplement), 41 (33.9%) completed the full study drug treatment duration (104 weeks), and 35 (28.9%) attended the follow-up visit 4 weeks (± 7 days) after stopping ivacaftor. Of the 80 participants who did not complete the study drug treatment, most (59 [73.8%]) discontinued study participation because they chose to receive commercially available ivacaftor, which had become available.

Most participants who rolled over from Study 110 had an *F508del-R117H-CFTR* genotype. Participants who rolled over from Study 111 and Study 113 had a variety of gating and residual function mutations, respectively, with no single dominant genotype; more than half of participants rolling over from Study 111 and Study 113 carried *F508del* on the second allele. A complete list of *CFTR* mutations in the FAS is shown in Table S2 in the supplement.

Safety Outcomes (Primary Endpoint)

Ivacaftor was generally safe and well tolerated in this study. Most participants experienced ≥ 1 AE (Table 2). The most common treatment-emergent AEs were infective PEx of CF (46.3%), cough (33.9%), headache (19.0%), sinus congestion and sputum increased (18.2% each), nasopharyngitis (17.4%), and sinusitis (15.7%). Among the 27 participants who experienced serious AEs (SAEs), two had SAEs that were considered related to the study drug (Table 2). SAEs occurring in > 1 participant were infective PEx of CF ($n = 21$ [17.4%]), gastroenteritis ($n = 2$ [1.7%]), and pneumonia ($n = 2$ [1.7%]). Three participants (2.5%) discontinued due to AEs. No deaths occurred. No clinically relevant trends in clinical laboratory test results attributable to ivacaftor treatment were apparent. Elevated transaminase levels were infrequent (Table S3 in the supplement).

Secondary Efficacy Results

Given the differences in *CFTR* genotypes across the parent studies, data are presented by parent-study subgroups to provide a better understanding of efficacy by mutation type.

Improvements in ppFEV₁ (LS mean absolute changes from baseline) were generally stable and durable over time during the 104 weeks of treatment, with an increase in variability in the magnitude of response during the latter part of the treatment period associated with the decreased number of participants (Fig. 2). However, the overall pattern of effects was consistent with results from the parent studies (Table S4 in the supplement).

In the 30 participants who completed the follow-up visit with a ppFEV₁ measure, the gains in ppFEV₁ during the treatment period trended back to pretreatment baseline levels in the 4-week follow-up period when they were no longer receiving ivacaftor.

LS mean changes from baseline in sweat chloride concentration varied considerably across parent-study subgroups (Fig. 3), with a robust response observed in participants from Study 111, a more modest response in

Table 1 Baseline participant demographics and characteristics by parent-study subgroup

Characteristic	Study 110 <i>R117H</i> ^a (<i>n</i> = 65)	Study 111 Gating ^b (<i>n</i> = 35)	Study 113 RF ^c (<i>n</i> = 21)	All participants (<i>N</i> = 121)
Male, <i>n</i> (%)	28 (43.1)	22 (62.9)	10 (47.6)	60 (49.6)
White, <i>n</i> (%)	65 (100.0)	32 (91.4)	21 (100.0)	118 (97.5)
Age				
Mean (SD), years	32.4 (16.9)	23.9 (13.6)	40.0 (13.5)	31.3 (16.3)
6 to 11 years, <i>n</i> (%)	13 (20.0)	8 (22.9)	0	21 (17.4)
12 to 17 years, <i>n</i> (%)	2 (3.1)	8 (22.9)	1 (4.8)	11 (9.1)
≥ 18 years, <i>n</i> (%)	50 (76.9)	19 (54.3)	20 (95.2)	89 (73.6)
ppFEV ₁				
Mean (SD), percentage points	71.8 (20.4)	78.3 (21.1)	62.8 (22.2)	72.1 (21.4)
< 70%, <i>n</i> (%)	29 (44.6)	12 (34.3)	15 (71.4)	56 (46.3)
≥ 70% to ≤ 90%, <i>n</i> (%)	23 (35.4)	10 (28.6)	3 (14.3)	36 (29.8)
> 90%, <i>n</i> (%)	13 (20.0)	13 (37.1)	3 (14.3)	29 (24.0)
BMI, mean (SD), kg/m ²	23.8 (5.6)	23.2 (5.3)	24.8 (5.8)	23.8 (5.5)
Sweat chloride concentration, mean (SD), mmol/l	60.9 (19.4) ^d	80.2 (22.8) ^e	55.7 (22.2)	65.6 (22.9) ^f

BMI body mass index, *ppFEV*₁ percent predicted forced expiratory volume in 1 s, *RF* residual function

^a Participants had an *R117H-CFTR* mutation

^b Participants had a non-*G551D-CFTR* gating mutation

^c Participants had phenotypic or molecular evidence of residual *CFTR* function

^d *N* = 59

^e *N* = 33

^f *N* = 113

participants from Study 110, and little to no response in participants from Study 113. There was a rapid improvement from baseline in CFQ-R RD score across all parent-study subgroups (Figure S2 in the supplement). The improvements in participant-reported respiratory symptoms were stable and durable over the 104 weeks of treatment. Data for LS mean rate of change in BMI over 104 weeks are shown in Table S5 in the supplement. A Kaplan–Meier plot of time to first PEx is shown in Figure S3 in the supplement.

DISCUSSION

Ivacaftor was well tolerated with no new safety concerns observed in pwCF aged 6 years and older with non-*G551D-CFTR* gating mutations, the *R117H-CFTR* mutation, or other residual function mutations. Safety results were consistent with ivacaftor's well-established safety profile demonstrated in clinical studies and by real-world evidence [2–11].

Ivacaftor showed durable clinical benefit across the three parent-study subgroups, improving lung function, sweat chloride concentration, and CFQ-R RD scores for up to 2 years of treatment. On average, BMI showed a

Table 2 Safety summary of adverse events

<i>n</i> (%)	Overall (<i>N</i> = 121)
Participants with any AEs	117 (96.7)
AEs related to the study medication ^a	24 (19.8)
AEs leading to death	0
Participants with any SAEs	27 (22.3)
SAEs related to the study medication ^b	2 (1.7)
AEs leading to study drug interruption	19 (15.7)
AEs leading to study drug withdrawal	3 (2.5)
AEs occurring in $\geq 10\%$ of participants	
Infective PEx of CF	56 (46.3)
Cough	41 (33.9)
Headache	23 (19.0)
Sinus congestion	22 (18.2)
Sputum increased	22 (18.2)
Nasopharyngitis	21 (17.4)
Sinusitis	19 (15.7)
Oropharyngeal pain	18 (14.9)
Viral upper respiratory tract infection	17 (14.0)
Nasal congestion	17 (14.0)
Constipation	17 (14.0)
Diarrhea	17 (14.0)
Pyrexia	17 (14.0)
Upper respiratory tract infection	15 (12.4)
Abdominal pain	13 (10.7)

AE adverse event, *CF* cystic fibrosis, *PEx* pulmonary exacerbation, *SAE* serious adverse event

^a Includes AEs deemed “related” or “possibly related” to the study medication

^b One possibly related SAE of infective PEx of CF, and one possibly related SAE of sinusitis

robust increase over 2 years in participants 18 years and older in parent-study subgroup 110. For other parent-study subgroups, the sample sizes were too low to interpret the numerically positive increases. Similarly, the sample sizes were too low to interpret BMI-for-age z-score (Table S5 in the supplement).

As CF is a chronic progressive disease, lung function is expected to decline (by approximately 1–3% per year) [15, 16] due to increasing age, number, and severity of PEx, nutritional status, presence of lung infections, and other factors. Despite this underlying progression, the magnitude of the increase in lung function in this long-term (up to 104 weeks) extension

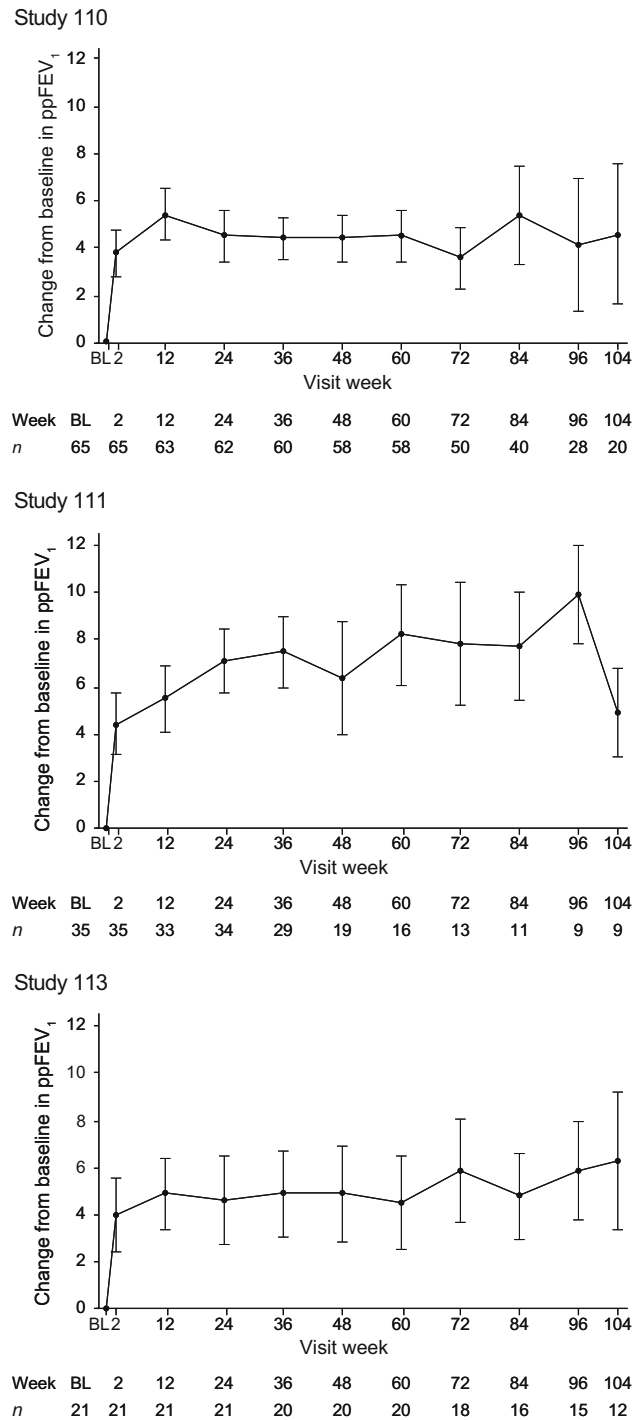


Fig. 2 Absolute change from baseline in ppFEV₁ in Extension Study 112 by parent-study subgroup. Data are least-squares means based on a mixed-effects model for

repeated measures, and *error bars* indicate standard errors. *BL* baseline, *ppFEV₁* percent predicted forced expiratory volume in 1 s

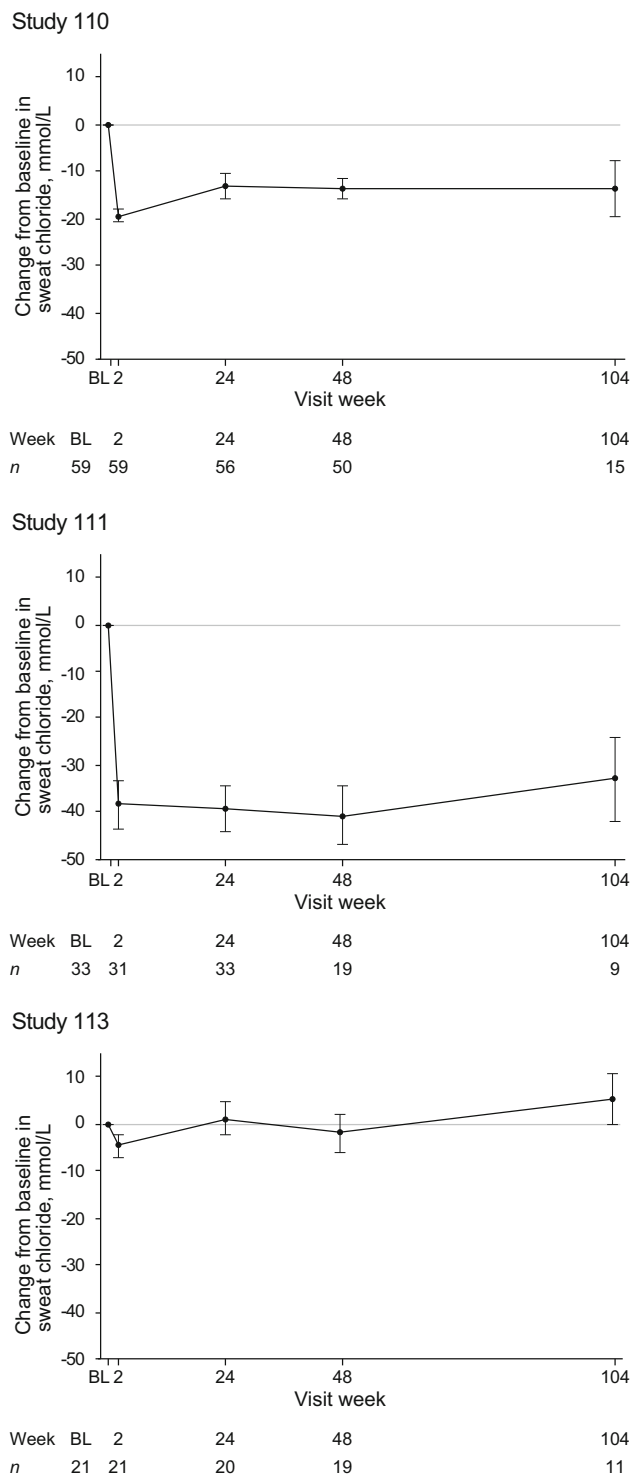


Fig. 3 Absolute change from baseline in sweat chloride concentration in Extension Study 112 by parent-study subgroup. Data are least-squares means based on a mixed-

effects model for repeated measures, and *error bars* indicate standard errors. *Solid gray line* (zero) represents no change from Extension Study 112 baseline. *BL* baseline

study is consistent with the expected outcomes based on data from the parent studies (110, 111, and 113). Moreover, outcomes from this extension study are consistent with outcomes from other long-term studies demonstrating that participants treated with ivacaftor have better-preserved lung function [4, 17].

The genotypes of participants in the parent-study subgroups are associated with different levels of CF severity, as seen by the higher baseline mean sweat chloride concentrations in participants from Study 111 and by the lower mean concentrations in Study 110 and Study 113; in Study 113, the mean sweat chloride concentration was below the 60 mmol/l diagnostic threshold (Table 1) [18]. These differences at baseline may have contributed to variations in response, which is consistent with the outcomes in the parent studies. For example, the magnitude of response in sweat chloride concentration was greatest in Study 111, in which participants had the highest baseline mean concentration.

This open-label extension study has several potential limitations. Using a voluntary rollover cohort risks introducing a selection bias. However, the extremely high participation rate (121/133 [91%]) suggests that any selection bias was limited. A further limitation is the lack of a comparator group, which can make the interpretation of outcomes more difficult. Moreover, almost half of the participants (59/121 [49%]) withdrew from the study because ivacaftor became commercially available to them. Despite this attrition, which increased variability and the impact of events such as PEx, the outcomes in this extension study are generally consistent with the results from the parent studies.

CONCLUSIONS

Ivacaftor was generally safe and well tolerated for up to 104 weeks of treatment in pwCF with ivacaftor-responsive mutations other than *G551D*. No new safety concerns were identified. The pattern of improvement across efficacy endpoints was durable and generally consistent with outcomes from the parent studies.

Collectively, these data suggest that ivacaftor is likely to significantly slow progression of CF lung disease and improve other long-term outcomes, including quality of life.

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Compliance with Ethics Guidelines. This study was conducted in accordance with good clinical practices, as described in the International Council for Harmonisation guidelines, and is consistent with the World Medical Association Declaration of Helsinki and applicable regional laws and regulations. The study protocol, informed consent form, and other necessary documents were reviewed and approved by an independent ethics committee or institutional review board for each study site before initiation of the study at that site (Table S1 in the supplement). Written informed consent was obtained from or for (with assent, where applicable) each participant on (or before) the day 1 visit.

Data Availability. Vertex is committed to advancing medical science and improving patient health. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.

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