Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the *G551D* mutation. N Engl J Med 2011;365:1663-72.

SUPPLEMENTARY APPENDIX

"A CFTR Potentiator in Patients with Cystic Fibrosis Who Have the G551D Mutation"

Ramsey BW, Davies J, McElvaney NG et al.

CONTENTS

DETAILED METHODOLOGY

Subjects

Eligible subjects had to have a confirmed diagnosis of CF,[1] accompanied by either chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities and a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis on at least one occasion. Subjects were required to have the *G551D-CFTR* mutation on at least one *CFTR* allele. CFTR genotype confirmation was performed using a 32 mutation panel (Ambry Genetics). Full gene sequencing was performed on samples where the mutation panel did not identify two CFTR mutations.

At screening, subjects had to be ≥12 years of age and demonstrate an FEV_1 of 40-90% of predicted value for age, gender, and height (Knudson standards[2]). Subjects were excluded if they had other illnesses that confounded the study results; ongoing illness; a pulmonary exacerbation or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before first dose of study drug; abnormal liver function tests, defined as 3 or more LFT parameters >3 times the upper limit of normal; or abnormal renal function tests. Subjects were also excluded if they had a history of prolonged QT/QTc interval; history of solid organ or hematological transplantation; colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *B. cenocepacia, B. dolosa,* and *M. abcessus*); concomitant use of any inhibitors or inducers of CYP3A4; or use of inhaled hypertonic saline treatment. Subjects were required to stop inhaled hypertonic saline treatment for at least 4 weeks prior to Day 1 (first dose of study drug).

Treatment Adherence

To ensure treatment adherence, site personnel reviewed study drug dosing requirements with the subject at each study visit. Compliance was also confirmed by ongoing drug accountability.

Endpoints

The primary efficacy endpoint was the absolute change in percent predicted FEV_1 from baseline through Week 24. Secondary endpoints included change from baseline in percent predicted FEV_1 through Week 48, time-to-first pulmonary exacerbation through Weeks 24 and 48, subject-reported respiratory symptoms through Weeks 24 and 48 as measured by the Cystic Fibrosis Questionnaire-Revised (CFQ R), change from baseline in weight at Weeks 24 and 48, and changes from baseline in sweat chloride concentration, a biomarker of CFTR channel function. Tertiary efficacy endpoints included duration of pulmonary exacerbations, duration of hospitalizations and duration of antibiotic therapy for

sinopulmonary signs/symptoms. The study also evaluated the safety and adverse event profile of ivacaftor.

Spirometry was performed according to American Thoracic Society guidelines.[3] Assessments were to be performed prior to the use of bronchodilators (at least 4 hours since last short-acting β-agonist or anticholinergic, 12 hours since last long-acting treatment, and 24 hours since the last once-daily treatment) and prior to study drug administration on the day of the visit. FEV_1, forced vital capacity (FVC), and forced midexpiratory flow rate ($FEF_{25-75\%}$) were determined. Values were recorded as volumes (L) for FEV_1 and FVC or rate (L/s) for $FEF_{25-75\%}$ and as percent predicted for age, gender, and height.[2]

Time-to-first pulmonary exacerbation was evaluated as a secondary efficacy measure. Pulmonary exacerbation in this study was defined using a modified Fuchs criteria of new or a change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following symptoms: new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection.[4] A subject with no events before withdrawal or completion of the study period was considered censored at the time of withdrawal or completion of the study period.

Subject-reported respiratory symptoms were assessed using the Respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a disease-specific health-related quality of life questionnaire.[5] The CFQ-R was administered to subjects prior to administration of study drug and any other assessment at the visit. The adult/adolescent or child versions of the CFQ-R were administered as appropriate. The primary analytical focus was determined *a priori* to be the respiratory health domain using a pooling of all self-response questionnaire versions (e.g., Adult/Adolescent and Child versions). Responses are provided on a 4-point Likert scale and rescaled within each domain to a score range from zero to 100 points. Higher scores represent better health.

Weight was measured with shoes off and before the morning dose of study drug.

Sweat testing was determined by pilocarpine iontophoresis and samples were collected using an approved Macroduct® (Wescor, Logan UT) collection device as described previously.[6] Sweat samples were sent to a central laboratory for testing and interpretation of results (University of Colorado). The sweat test was

conducted within a window of ±2 hours relative to the morning dose of study drug except for the first study day, when the sweat chloride test was performed prior to the dose and may have been done the previous day.

Safety was evaluated by assessment of adverse events, clinical laboratory tests, standard digital electrocardiograms (ECGs), 24-hour ambulatory ECGs, vital signs, and physical examinations.

The only pre-specified criterion for drug interruption was elevated liver enzymes: ALT or AST >8 × ULN; ALT or AST >5 × ULN for more than 2 weeks; total bilirubin >2 × ULN and/or clinical jaundice, in association with elevation of ALT; AST >3 × ULN.

Predefined criteria for study drug withdrawal included:

- A female subject has a confirmed pregnancy or, in the case of male subjects, their female partner becomes pregnant.
- A subject's study treatment assignment becomes unblinded to the subject, the site staff, or the blinded Vertex staff.
- A subject experiences an arrhythmia or conduction abnormality, including but not limited to prolonged QTcF interval, where the severity is categorized as CTCAE Grade 3 or higher.
- A subject experiences an elevated alanine transaminase (ALT) or aspartate transaminase (AST) of >8 × ULN; or ALT or AST >5 × ULN for more than 2 weeks; or total bilirubin >2 × ULN and/or clinical jaundice, in association with elevation of ALT and AST >3 × ULN.
- And no convincing alternative etiology (e.g., viral hepatitis, alcohol ingestion) for the elevated transaminase is identified, regardless of whether ALT or AST levels had improved

Statistical Analyses

Primary analysis for absolute change from baseline in percent predicted FEV_1 through Week 48, absolute change from baseline in CFQ-R score, and absolute change from baseline in sweat chloride was similar to that of the primary efficacy endpoint (i.e., based on a Mixed-Effects Model for Repeated Measures [MMRM]). However, change from baseline in weight was analyzed using a linear mixed effect (LME) model and time to first pulmonary exacerbation was analyzed using Cox regression and Kaplan-Meier methods. Descriptive statistics (raw values) were summarized for chemistry, hematology, vital signs, and ECG parameters.

To control the overall type I error rate, the primary and key secondary endpoints (absolute change from baseline in pooled respiratory CFQ-R score through Week 24, absolute change from baseline in sweat chloride through Week 24, time to first pulmonary exacerbation through Week 48, and absolute change from baseline in weight at Week 48) were analyzed using the following multi-stage gate keeping procedure:

1. The primary efficacy endpoint was tested at significance level $\alpha = 0.05$.
2. If a statistically significant result was obtained from test 1, absolute change from baseline in CFQ-R respiratory domain score through Week 24 and change from baseline in sweat chloride through Week 24 was tested using Hochberg's step-up procedure at significance level $\alpha = 0.05$.
3. If a statistically significant result was obtained from test 2, time-to-first pulmonary exacerbation through Week 48 and change from baseline in weight at Week 48 was tested using Hochberg's step-up procedure at significance level $\alpha = 0.05$.

Based on this testing procedure and the obtained nominal *P*-values, the primary endpoint and all the 4 key secondary endpoints were statistically significant. All other analyses of secondary, tertiary, and exploratory efficacy endpoints were not controlled for type I error. That is, *P*-values reported for these endpoints which are <0.05 indicate nominal statistically significant results.

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Supplemental Table 1. Summary of results through 24 and 48 weeks.

	Week 24			Week 48		
Endpoint	**Ivacaftor (N=83)**	**Placebo (N=78)**	**Difference 95% CI p-value**	**Ivacaftor (N=83)**	**Placebo (N=78)**	**Difference 95% CI p-value**
FEV_1 % predicted absolute change from baseline, mean	10.4	-0.2	10.6% (8.6,12.6) *P*<0.0001	10.1	-0.4	10.5% (8.5, 12.5) *P*<0.0001
FEV_1 (L) change from baseline, mean	0.4	0.0	0.4 (0.3, 0.4) *P*<0.0001	0.4	0.0	0.4 (0.3, 0.4) *P*<0.0001
FEV_1 relative change from baseline , mean	17.6	0.7	16.9 (13.6, 20.2) *P*<0.0001	17.5	0.8	16.8 (13.5, 20.1) *P*<0.0001
Sweat chloride (mmol/L) change from baseline, mean	-48.7	-0.8	-47.9 (-51.3, -44.5) *P*<0.0001	-48.7	-0.6	-48.1 (-51.5, -44.7) *P*<0.0001
Pulmonary exacerbations, No. subjects	18	35	Rate ratio 0.38 (0.22, 0.64) *P*=0.0003	28	44	Rate ratio 0.43 (0.27, 0.68) *P*=0.0003
Weight (kg) change from baseline , mean	3.0	0.2	2.8 (1.8, 3.7) *P*<0.0001	3.1	0.4	2.7 (1.3, 4.1) *P*<0.0001

Supplemental Table 2. Rate and duration of pulmonary exacerbations and associated events through Week 48.

2A. Rate of event occurrence through Week 48*, n (rate per subject)

Event Type	Placebo (N=78)	Ivacaftor (N=83)	p-value
Pulmonary exacerbation	99 (1.38)	47 (0.59)	0.0003
Pulmonary exacerbation requiring hospitalization	31 (0.49)	21 (0.31)	0.1948
Pulmonary exacerbation requiring IV antibiotics	47 (0.71)	28 (0.40)	0.0776

*****Estimates were obtained from negative binomial

2B. Normalized total time with events through Week 48*, mean (SD), days

Event Type	Placebo (N=78)	Ivacaftor (N=83)	p-value[†]
Days with pulmonary exacerbations	36.7 (49.5)	13.5 (27.3)	0.0007
Days hospitalized for pulmonary exacerbations	4.15 (8.71)	3.92 (13.62)	0.0275
Days with IV antibiotics administered for pulmonary exacerbations	11.03 (20.36)	6.68 (19.43)	0.0183

*Days with events are normalized to time on study (i.e. 336 days for Week 48)

[†]P-values are from a stratified (by baseline % Predicted FEV_1 Severity and Age group) Wilcoxon rank-sum test

Supplemental Table 3. Adverse events leading to study drug interruption.

Ivacaftor Subjects

Subject	Adverse event
1	Hemoptysis
2	Migraine
3	Pulmonary exacerbation Anaphylactic shock
4	Lymph node pain Gynecomastia
5	Pulmonary exacerbation
6	Hepatic enzyme increased
7	Hepatic enzyme increased
8	Vulvovaginal mycotic infection Oral candidiasis Pulmonary exacerbation Pulmonary exacerbation
9	Myalgia Diarrhea
10	Upper respiratory tract infection
11	Weight decreased Pulmonary exacerbation

No subjects discontinued treatment after drug interruption

Placebo Subjects

Subject	Adverse event
1	Blood lactate dehydrogenase increased Hepatic enzyme increased
2	Migraine
3	Pulmonary exacerbation
4	Rash Nephrolithiasis Renal colic
5*	Vomiting Respiratory distress

*Subject subsequently discontinued treatment after drug interruption

Supplemental Table 4. Adverse events occurring in ≥ 10% in either treatment group through Week 48.

Adverse event, n (%)	Placebo (N=78)	Ivacaftor (N=83)
Pulmonary exacerbation*	50 (64.1)	34 (41.0)
Cough	33 (42.3)	27 (32.5)
Headache	13 (16.7)	19 (22.9)
Upper respiratory tract infection	12 (15.4)	19 (22.9)
Oropharyngeal pain	15 (19.2)	17 (20.5)
Nasal congestion	12 (15.4)	17 (20.5)
Abdominal pain	10 (12.8)	13 (15.7)
Nausea	9 (11.5)	13 (15.7)
Productive cough	11 (14.1)	12 (14.5)
Rash	4 (5.1)	12 (14.5)
Diarrhea	10 (12.8)	11 (13.3)
Dizziness	1 (1.3)	10 (12.0)
Nasopharyngitis	10 (12.8)	10 (12.0)
Pyrexia	9 (11.5)	10 (12.0)
Hemoptysis	17 (21.8)	9 (10.8)
Rales	8 (10.3)	9 (10.8)
Vomiting	10 (12.8)	9 (10.8)
Pulmonary function test decreased	11 (14.1)	3 (3.6)

*coded as Cystic fibrosis lung

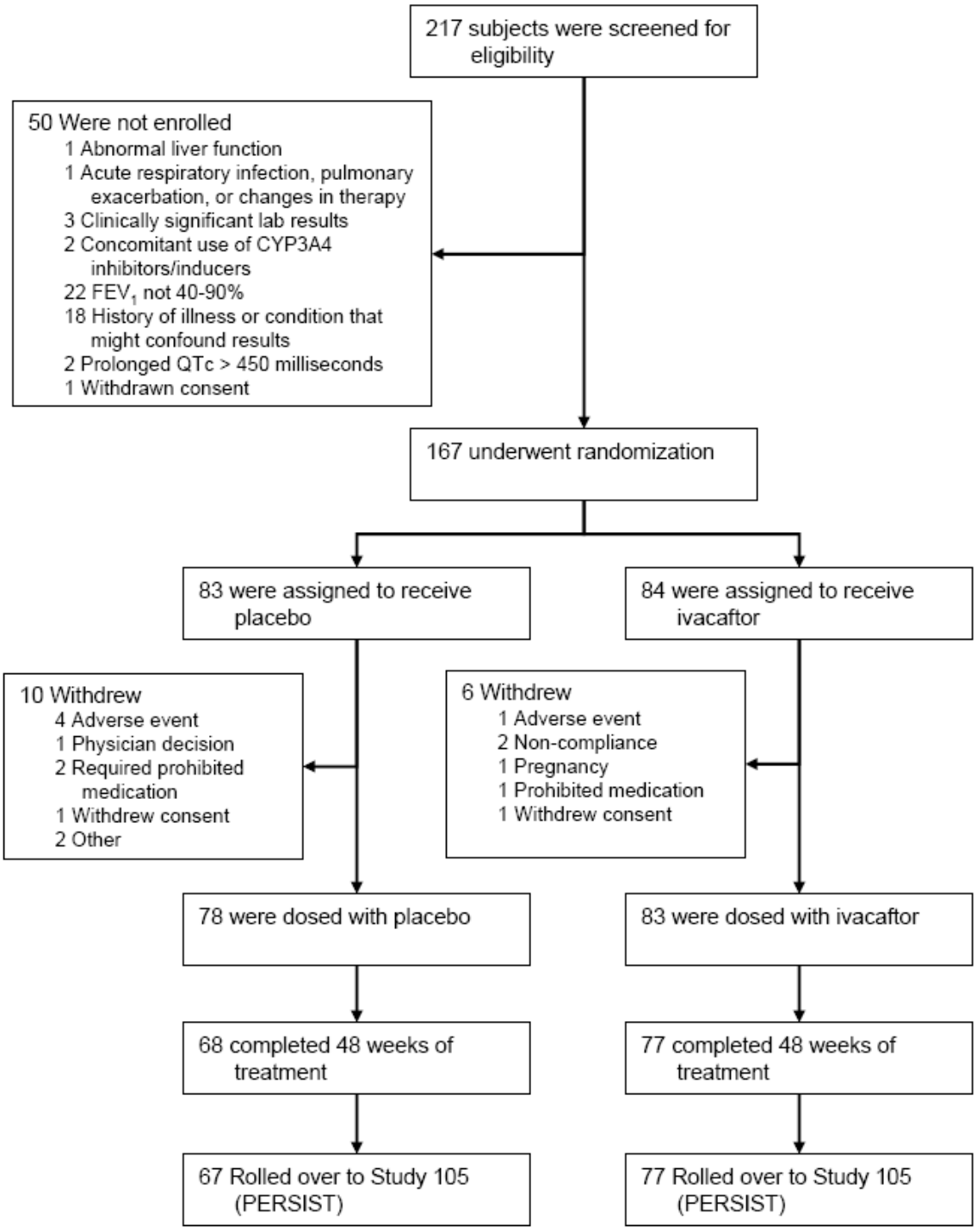
Supplemental Table 5. Maximum liver function test abnormalities during treatment through Week 48.

Maximum Result	Placebo (N=78) n (%)	Ivacaftor (N=83) n (%)
2x to 3x ULN		
AST	4 (5.1)	8 (9.6)
ALT	6 (7.7)	5 (6.0)
Bilirubin	1 (1.3)	2 (2.4)
3x to 5x ULN		
AST	2 (2.6)	1 (1.2)
ALT	2 (2.6)	0
Bilirubin	0	0
5x to 8x ULN		
AST	0	1 (1.2)
ALT	1 (1.3)	0
Bilirubin	0	0
8x ULN		
AST	1 (1.3)	1 (1.2)
ALT	0	3 (3.6)
Bilirubin	0	0

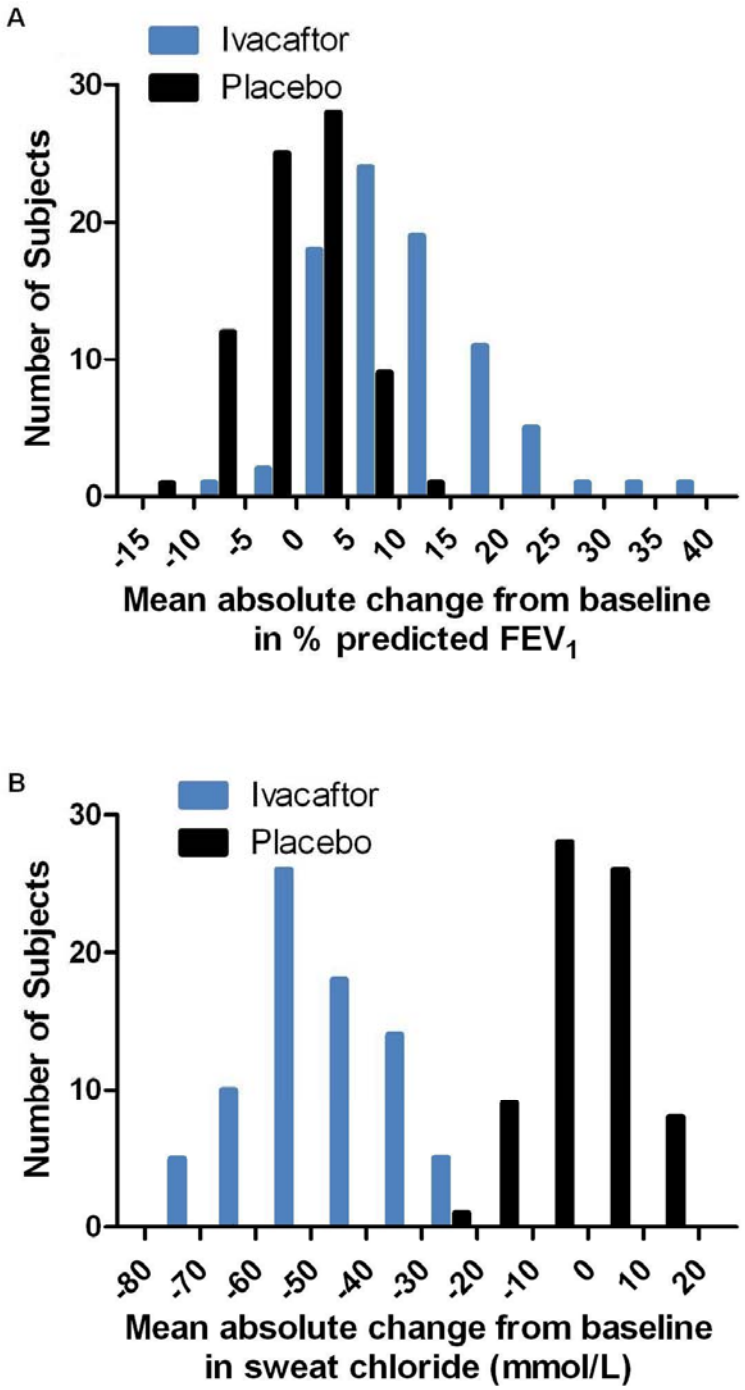
Supplemental Table 6. Chronic medications utilized prior to the study.

Medication, n (%)	Placebo (N=78)	Ivacaftor (N=83)
Dornase alfa	57 (73.1)	54 (65.1)
Azithromycin	50 (64.1)	51 (61.4)
Salbutamol	56 (71.8)	53 (63.9)
Inhaled tobramycin	35 (44.9)	28 (33.7)
Fluticasone-salmeterol	32 (41.0)	23 (27.7)
Ibuprofen	9 (11.5)	14 (16.9)
Inhaled colistin	5 (6.4)	9 (10.8)
Montelukast sodium	13 (16.7)	5 (6.0)
Inhaled aztreonam	0	1 (1.2)

Supplemental Figure 1. Subject disposition.

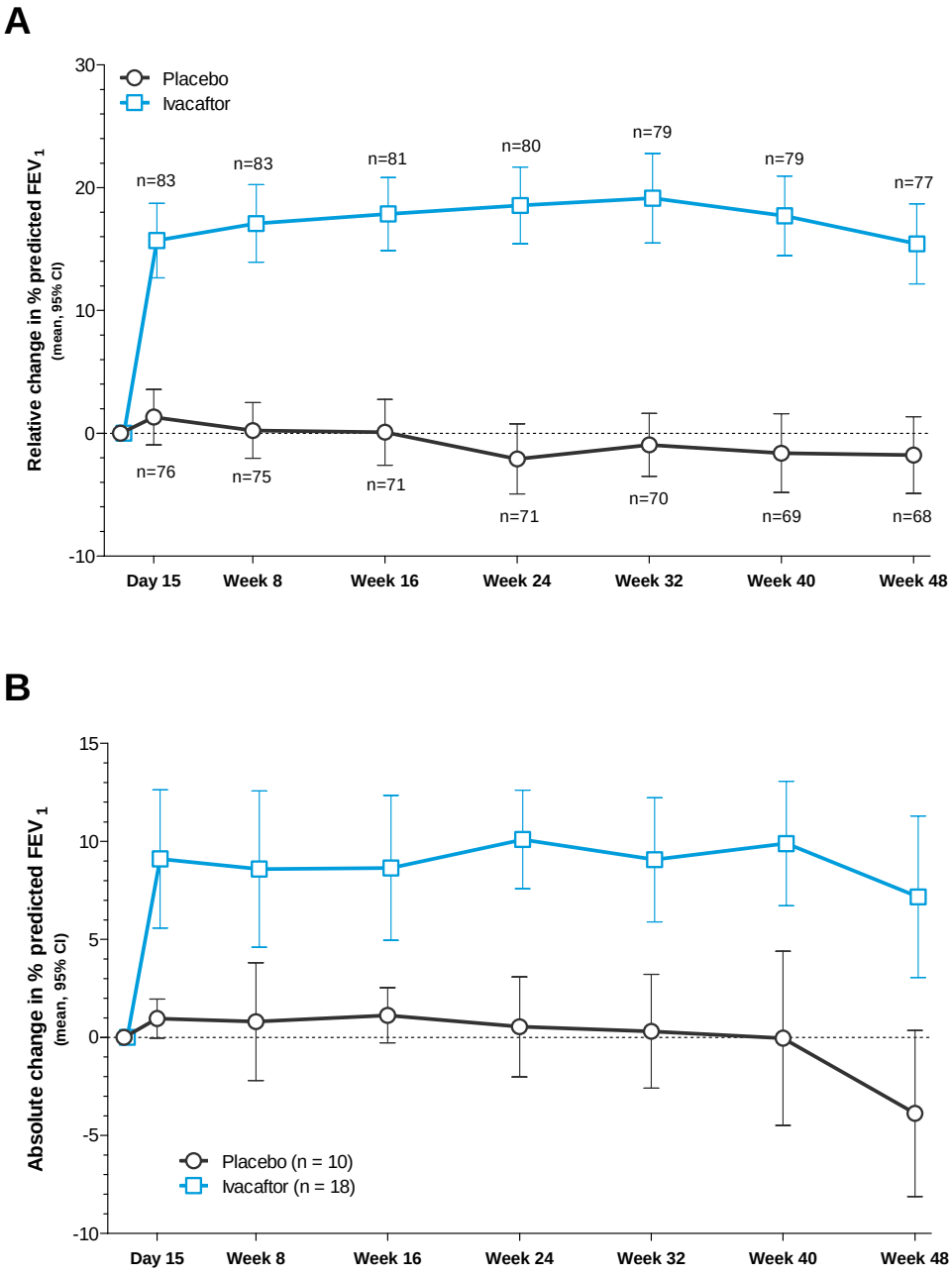


Supplemental Figure 2. Distribution of responses. Panel A shows the absolute change from baseline in FEV_1 response through 24 weeks. Panel B shows the absolute change from baseline in sweat chloride response through 24 weeks.



Counts displayed as bars include results on the upper boundary and exclude results on the lower boundary of the intervals

Supplemental Figure 3. FEV_1 additional analyses. Panel A shows the rrelative mean change from baseline (with 95% confidence intervals) in FEV_1 % predicted. Panel B shows the absolute mean change from baseline (with 95% confidence intervals) in FEV_1 % predicted for the subgroup of subjects with baseline predicted FEV_1 in the range of 40% to 50%, inclusive.



Supplemental Figure 4. Changes from baseline through Weeks 24 and 48 in additional spirometry parameters by treatment group. Panel A shows the absolute change from baseline in $FEF_{25-75\%}$, Panel B shows the absolute change from baseline in FVC. Panel C shows the absolute change from baseline in the ratio of FEV_1/FVC.