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Effectiveness of ivacaftor in cystic fibrosis Patients with non-*G551D* gating mutations

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Abstract

Background—The cystic fibrosis transmembrane conductance regulator (CFTR) potentiator ivacaftor is approved for patients with CF with gating and residual function CFTR mutations. We report the results of an observational study investigating its effects in CF patients with non-*G551D* gating mutations.

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AUTHOR CONTRIBUTIONS

S.M.R., S.D.S., and S.L.H. designed the study. A.B., S.L.H. analyzed the data. G.M.S., J.S.G., S.M.R., A.B., and S.L.H. interpreted the data. J.S.G., A.B., S.L.H. G.M.S. and S.M.R. prepared the manuscript. All authors reviewed the manuscript and approved of the final version of the manuscript before submission.

CONFLICTS OF INTEREST

SMR serves as an investigator and consultant to Vertex Pharmaceuticals, the manufacturer of ivacaftor, on the design and conduct of CF clinical trials. GMS serves as an investigator on studies conducted by Vertex Pharmaceuticals.

Methods—Patients with non-*G551D* gating mutations were recruited to an open-label study evaluating ivacaftor. Primary outcomes included: lung function, sweat chloride, weight gain, and quality of life scores.

Results—Twenty-one subjects were enrolled and completed 6 months follow-up on ivacaftor; mean age was 25.6 years with 52% <18. Baseline ppFEV₁ was 68% and mean sweat chloride 89.6 mEq/L. Participants experienced significant improvements in ppFEV₁ (mean absolute increase of 10.9% 95% CI= [2.6,19.3], p=0.0134), sweat chloride (−48.6 95% CI= [−67.4, −29.9], p<0.0001), and weight (5.1 kilograms, 95% CI= [2.8, 7.3], p=0.0002).

Conclusions—Patients with non-*G551D* gating mutations experienced improved lung function, nutritional status, and quality of life. This study supports ongoing use of ivacaftor for patients with these mutations.

Keywords

ivacaftor; gating mutation; CFTR potentiator; Clinical Trials

Introduction

Cystic fibrosis (CF) is a rare, autosomal recessive genetic disorder caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene that encodes a transmembrane protein, responsible for chloride and bicarbonate conductance [1]. Mutations in *CFTR* result in epithelial dysfunction in a variety of tissues due to imbalance in ion and fluid homeostasis. In the lung, this imbalance results in viscous secretions that impairs normal mucociliary clearance, promoting progressive pulmonary decline and infections that result in respiratory failure and death [2].

Recent developments have resulted in a new class of drugs that target the defect in the protein, called *CFTR* modulators, the first of which is the CFTR potentiator ivacaftor [3–5]. As a CFTR potentiator, ivacaftor targets CFTR protein on the apical membrane of epithelial cells, to augment open probability and enhance the transport of chloride and bicarbonate anions. CFTR potentiators are particularly active in vitro for CFTR mutations that exhibit disrupted ATP-dependent channel gating, preventing efficient ion channel opening. These ‘gating’ mutations are classically grouped as molecular Class III, among the over 1900 *CFTR* variants, [6, 7] noting that many variants can also exhibit other cellular abnormalities [8] such as abnormal processing or reduced surface stability. [9] The most common gating mutation is *G551D*, found in approximately 4.4% of all CF patients in the United States. Other mutations that principally induce severe gating defects include *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, and *G1349D* and are quite rare, making up only 1.6% of the population in the United States [10].

In CF patients with non-*G551D* gating mutations, a Phase 3 trial termed KONNECTION demonstrated improved spirometry, quality of life, and SC compared to placebo, resulting in FDA approval in this mutation group [11]. In the *G551D* Observational Study (GOAL)-Expanded to Additional Genotypes and Extended for Long Term Follow up (GOAL-e²) to include recently approved non-*G551D* gating mutations, we studied the effectiveness of six

months of ivacaftor in patients age 6 years and older with at least one non-*G551D* gating allele, expanding beyond a clinical trial in this population[12] and including additional outcomes of hospitalization events and culture results.

Methods

Study design and participants

The original GOAL longitudinal cohort study design and analysis of the first cohort of participants (those with at least one *G551D* allele) have been summarized elsewhere [13]. The study was subsequently expanded to include Cohort 3, an additional cohort of participants age 6 and above with at least one non-*G551D* gating mutation, any mutation on the second allele except *G551D* or R117H, and no prior exposure to ivacaftor (<http://clinicaltrials.gov/ct2/show/NCT01521338>). Patients with G970R, which was presumed to be a gating mutation based on initial electrophysiological investigation in Fisher rat thyroid (FRT) cells but was later identified as a splice variant in non-heterologous cells systems including primary epithelium [14], were thus excluded from further study. Study procedures were conducted as previously described [13]. Briefly, subject data were collected at baseline and at 1, 3, and 6 months after starting ivacaftor. As previously described [13], additional clinical data from the US CF Foundation Patient Registry (CFFPR) were also evaluated in this study population. Written informed consent was obtained from patients and/or guardians according to each study site's Institutional Review Boards.

Procedures and outcome measures

Study assessments conducted for all enrolled participants included: forced expiratory volume over one second (FEV₁, L), FEV₁ percent of predicted, weight (kilograms or percentiles for those < 20 years old), height (cm or percentiles for those < 20 years old), Body Mass Index (kg/m² and percentiles for those < 20 years old), sweat chloride (SC, mEq/L), Cystic Fibrosis Questionnaire-Revised (CFQ-R) [15], Sino-Nasal Outcome Test-20 (SNOT-20) [16] score, and Cystic Fibrosis Respiratory Symptom Diary (CFRSD) [17] score. Hospitalization events and *P. aeruginosa* cultures results were ascertained via merged CFFPR data. Spirometry was performed according to American Thoracic Society standards [18] and percent of predicted values were calculated using reference equations [19, 20]. In addition, biological samples for future research (plasma, serum, buffy coat, urine, and expectorated sputum) were collected and stored at the CFFT Biorepository.

Statistical Analyses

Unless otherwise noted, continuous outcomes are summarized using paired mean changes and standard deviations [SD] from baseline with corresponding 95% confidence intervals (CI) and paired t-tests. Cross-sectional differences in proportions were compared using Fisher's exact test and paired differences in proportions were assessed with McNemar's test. Hospitalization rates (adjusted for participant follow-up) were compared with Wilcoxon's sign test. Pearson's correlation coefficient was used to explore associations between changes in SC and changes in clinical measures. Reported p-values are two-sided and a 0.05 level of significance was used. Analyses were performed using SAS (version 9.4, Cary, NC), and R (version 3.3, Vienna, Austria).

Results

Patient population

Twelve centers within the Cystic Fibrosis Therapeutics Development Network enrolled non-*G551D* gating mutation participants between February 2014 and January 2016. Of 24 patients with one of 8 eligible gating mutations, 23 were enrolled in the study and completed follow up. Of these, 21 were prescribed ivacaftor as part of this observational study, whereas two patients declined ivacaftor. Eighteen (86%) completed the entire study with 180 days of follow up (Figure 1); two were lost to follow-up, and one withdrew. One subject had a lung transplant approximately 3 months after initiation of ivacaftor and therefore post-transplant measurements were excluded from the analysis.

Baseline characteristics and demographics of the analyzed population are described in Table 1. Ten subjects (48%) were 18 or older, and 11 subjects (52%) were 6-17 years of age. All patients had at least one non-*G551D* gating mutation, with the prevalence shown by CFTR mutation in *trans* in Table 1. Notably, three patients (one pediatric, two adult) possessed second alleles considered to have residual function which were recently approved for ivacaftor by the Food and Drug Administration; these alleles are expected to contribute to the response to ivacaftor, as well. One patient was homozygous for the S549R gating mutation and two patients had an unidentified second allele. Nine patients (43%) were Black or Hispanic, indicating a more diverse racial balance compared to other CF studies and the underlying prevalence of these rare mutations.

The baseline ppFEV₁ of subjects enrolled who were prescribed ivacaftor (n=21) was 68.0% (Supplemental Table 1). There were some differences based on age; the baseline ppFEV₁ in the pediatric group (age < 18) was 88.7 while the adult group was 45.2 (Supplemental Table 2). The baseline BMI was 20.8 Kg/m² (26.6 percentile) and the mean baseline SC was 89.6 mmol/L. The baseline ppFEV₁ values for the two subjects who enrolled but ultimately chose not to take ivacaftor (and thus were excluded from analysis) were 80.9 and 123.2.

Effect of ivacaftor on lung function

Effects on lung function at each time point are summarized for the overall cohort in Supplementary Table 1 and by age (≥ 18 yo or < 18 yo) in Supplementary Table 2. Among enrolled subjects prescribed ivacaftor, there was a mean absolute increase in ppFEV₁ of 9.3% [4.2, 14.4] at one month (p=0.0011), which was sustained at three (+8.4 [1.4, 15.4], p=0.0214) and six month (+10.9 [2.6, 19.3], p=0.0134) follow-up visits (Figure 2A). Non-significant improvement in percent predicted Forced Vital Capacity (FVC) of 6.5 [-1.8, 14.8] was also observed at six months (p=0.1170; Table S2).

The absolute increase in ppFEV₁ diverged in the pediatric age group compared to the adult group, although this did not reach statistical significance on direct comparison (mean difference of -10.4 [-27.4, 6.6], p= 0.2103). In pediatric subjects, there was a mean absolute increase in ppFEV₁ of 6.1 [-4.1, 16.2] at six months (p=0.2058); whereas, adult subjects experienced an increase of 16.4 [1.1, 31.8] that was a statistically significant change from baseline (p=0.0393, Supplementary Table 2). Pediatric subjects reached normalized ppFEV₁ (achieving a mean ppFEV₁ of 94.6% at 6 months with 76% of patients exceeding 100%

predicted), whereas adults had a mean ppFEV₁ of 63.1%, at 6 months post ivacaftor at the time of study completion.

Effect of ivacaftor on nutritional status

Effects on nutritional status at each time point are summarized for the overall cohort in Supplementary Table 1 and by age (≥ 18 yo or < 18 yo) in Supplementary Table 2. Participants experienced a significant improvement in nutritional status, with a mean BMI increase of 1.4 kg/m² ($p < 0.001$, Figure 2B) and weight of 5.1 kg ($p = 0.0002$) by six months. These results were of similar magnitude in children and adults. The pediatric group had a mean BMI gain of 1.3 kg/m² ($p = 0.0516$), weight gain of 5.8 kg ($p = 0.0123$), and height z-score of 0.2 ($p = 0.0179$) by six months while the adults had a mean weight gain of 4.3 kg ($p = 0.0046$) and BMI gain of 1.4 kg/m² ($p = 0.0042$). There was a 5-point increase in height percentile for subjects < 20 years of age at 6 months ($p = 0.0344$), while neither the weight percentiles nor the BMI percentiles exhibited statistically significant changes over the course of this study.

Effect of ivacaftor on SC

Figure 2C shows changes in SC over the course of the study and the effects on CFTR function at each time point are summarized for the overall cohort in Supplementary Table 1 and by age (≥ 18 yo or < 18 yo) in Supplementary Table 2. Overall, the SC significantly decreased by -53.5 mEq/L [-63.3, -43.7] at one month ($p < 0.0001$); -51.4 mEq/L [-63.2, -39.5] at three months ($p < 0.0001$); and -48.6 mEq/L [-67.4, -29.9] at six months ($p < 0.0001$). Baseline SC among all participants was 89.6 mEq/L; in the pediatric group this was 99.0 mEq/L, and the adults 79.2 mEq/L (mean difference = 19.7, $p = 0.0374$). Perhaps consequently, the pediatric group had a somewhat larger change in sweat chloride (SC) at all time points, as illustrated in a sustained, significant reduction at six months of -57.3 mEq/L [-85.5, -28.7] compared to -37.2 mEq/L [-67.5, -6.8] in adults (-20.1 mEq/L difference, p -value=0.2578).

Effect of ivacaftor on patient-reported quality-of-life instruments

In this study, the CFQR-Respiratory, CFRSD, and SNOT-20 were used to assess patient reported symptoms (Figure 2D). Effects on quality of life at each time point are summarized for the overall cohort in Supplementary Table 1 and by age (≥ 18 yo or < 18 yo) in Supplementary Table 2. While score improvements (indicating reduced symptoms) in all three instruments were reported at one month (CFQ-R-Respiratory improvement of +16.1 points, $p = 0.0035$; CFRSD reduction of -11.4, $p = 0.0154$; SNOT-20 reduction of -0.4, $p = 0.0098$), only improvement in CFQ-R was statistically significant at six months (improvement of 14.2 points, $p = 0.0366$).

The response in patient reported outcomes varied by age group. At baseline the pediatric and adult CFQ-R scores were discrepant, reflecting the overall better health of the pediatric population. The pediatric baseline score was 74.0 whereas the adult score was 48.9. The improvement above baseline reported by the adult group was larger at all time points (Supplementary Table 2). Similar trends were seen in the CFRSD, with a lower baseline score in children compared to adults, and a larger, although not statistically significant score

reduction by six months in adults (Supplementary Table 2). The ivacaftor response to SNOT-20 scores, in contrast, did not vary as widely between adults and children (Supplementary Table 2).

Effect of ivacaftor use on hospitalization frequency and isolation of *Pseudomonas aeruginosa* (*Pa*)

Data from the CFFPR were extracted to evaluate the effect of ivacaftor use on hospitalization rates and respiratory *Pa* isolation during the 6 month follow-up period as compared to findings prior to ivacaftor use. There was a mean of 16.7 months of follow-up data for subjects taking ivacaftor. Because of variation in clinical follow up (compared to the research visits) and data entry into CFFPR, not all subjects are included in all time-points. While the percent of participants hospitalized after ivacaftor initiation decreased following ivacaftor use (Figure 3A), these changes were not statistically significant. In the immediate 6 months prior to starting ivacaftor, 38% of participants were hospitalized; this decreased to 10% in the first 6 months after initiation of ivacaftor, a finding that was sustained for an additional 6 months. When adjusted for differential follow up, there was a statistically significant decrease in hospitalization rates post-ivacaftor initiation. On average, there were 1.05 hospitalizations/year before ivacaftor, 0.34 post-ivacaftor, and a paired rate reduction of 0.71 hospitalizations per participant-year (95% CI = [0.19-1.24], p-value = 0.004)

In the year prior to initiation of ivacaftor, approximately 50% of subjects had at least one culture positive for *P. aeruginosa* (Figure 3B). After initiation, 41% of participants had at least one positive culture in the first 6 months, while only 28% were positive 6-12 months after initiation of ivacaftor, although these changes were not statistically significant. The change at 6-12 months post initiation represents a 41.6% relative reduction in *P. aeruginosa* isolation compared to the same interval one-year prior. In *G551D* patients a 32.7% reduction was previously observed.¹⁸ Expectored sputum gradually made up a smaller proportion of the respiratory cultures over time, and consequently the use of oropharyngeal swabs increased during the study. 83% of samples were expectorated in -12 to -6 months pre-ivacaftor, and this sequentially diminished for each additional 6 month interval: 76%, 72%, and finally 60% in 6-12 months after initiation of ivacaftor, respectively; this may have been due to reductions in productive cough in the cohort with prolonged CFTR modulator therapy, as also experienced in *G551D* participants.[13, 21]

Discussion

In this six-month observational study, the effects of ivacaftor on patients with non-*G551D* gating mutations were beneficial and sustained over the course of 180 days. There were overall improvements in lung function, SC, weight, growth (height), quality of life, and number of hospitalizations (adjusted for differential follow up). The magnitude of response appears generally comparable to the *G551D* participants of the GOAL study [22], and the conclusions substantiate prior randomized controlled trials [12, 23, 24]. Supporting data previously observed in *G551D* participants, there was also a reduction in the prevalence of detectable *Pa* infection, although this did not achieve statistical significance.

The beneficial response to ivacaftor in non-*G551D* gating patients was not uniform, and appears to be age-related, in part, likely related in part to differences in baseline functional status of younger vs. older participants. The short-term improvement in lung function among all subjects in this study was greater (+9.3% at one month) than that reported in the KONNECTION (7.5% at 8 weeks) [12] study. When the adult participants of this study were analyzed separately, the improvement as compared to all subjects in KONNECTION was even larger (+16.4 at 6 months compared to +13.5 in the KONNECTION open label extension). As has been reported previously, the change in lung function among the pediatric group was less substantial, and may reflect the already high ppFEV₁ among that group. As a comparison, the ENVISION trial [23] enrolled patients with at least one *G551D* allele who were 6-11 years of age. These patients had a mean baseline ppFEV₁ of 84.7, and the mean absolute increase from baseline was 12.6 percentage points. In our study, the baseline ppFEV₁ was slightly higher (88.7), and the improvement in ppFEV₁ was slightly lower (6.1%).

The effect of ivacaftor in children <18y is less pronounced for lung function, CFQ-R, and CFRSD, possibly due to a ceiling effect on these parameters, while effects on SC are much greater. This emphasizes that SC has important limitations as a clinical biomarker to predict effects on ppFEV₁ across the entire spectrum of the CF patient population, and cannot be used on an individual basis for all patients [25–28]. In children, other modalities of lung function assessment, such as the lung clearance index (LCI), may be more applicable since this measure has been shown to be more sensitive to changes in lung function in children [29–31].

The differences in the two age groups are also pronounced with respect to changes in sweat chloride. When compared to other clinical trials in pediatric gating mutation patients, the baseline sweat chloride and change in sweat chloride with ivacaftor treatment were comparable to sweat chloride values observed in other ivacaftor trials [23, 29, 32]. In contrast, the adult patients had a relatively lower baseline sweat chloride, probably due to the small sample size in the study. While this differs from previous controlled trials, we nevertheless observed that the sweat chloride achieved following ivacaftor treatment as similar to previously published values, suggesting a similar degree of CFTR modulation [5]. We also speculate that differences in the change in sweat chloride between age groups may be due to variable pharmacokinetics of CFTR modulators between children and adults.

Our study was limited by a small sample size, reflecting the paucity of non-*G551D* gating mutations amongst patients with CF. Three subjects had a residual function mutation on the alternate allele that are known to respond to ivacaftor, and one subject was homozygous for a non-*G551D* gating mutation, which may also affect results, potentially augmenting response beyond the single gating allele. Small sample size, for example, is probably responsible for a relatively low baseline sweat chloride in the adult subjects studied and apparent differences in changes in sweat chloride marking response to CFTR modulation. The study is an observational study, and all data are derived from patients who were on ivacaftor – there is no placebo group for comparison. Importantly, 64.6% of pediatric participants are in the pubertal range (12-17 years), which may impact the growth velocity during this time frame, but would be expected to be enhanced by ivacaftor use, as reported previously [33]. All

participants were unblinded and aware that they were on the study drug, which could influence subjective responses on the CFQR, SNOT-20 and CFSRD scores. Notably, the response rates in the ENVISION study (children, 5.9) [23]; PERSIST (maximum of 10.8 from all groups) [24]; and KONNECTION (adults, 9.6) [12] were all lower than the improvement seen in this study among similar patients, which may reflect this bias.

We acknowledge limitations in the data collection for rates of exacerbations and *Pa* culture positivity. As these data were derived from CFFPR, inherent bias toward treatment effect in the setting of unblinded treatment may have falsely reduced hospitalizations. Nevertheless, the findings were consistent with a previous cohort of G551D patients, and were sustained over one year of observation. While changes in *Pa* status were not statistically significant, probably due to the small sample size, the proportional reduction in *Pa* positivity was highly consistent with our previous report in G551D patients [22] and is supported by mechanistic data indicating reduced bacterial survival upon ivacaftor administration.[34]

In this study, ivacaftor resulted in improvements in multiple parameters in our patient population with non-*G551D* gating mutations. These improvements were sustained and significant over the course of the entire observation period, supporting the continued use of ivacaftor in both adult and pediatric patients with these alleles. In particular, the treatment of young children suggests the possibility of significantly modifying their lifelong disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CFTR Cystic Fibrosis Transmembrane conductance regulator

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Highlights

- Twenty-one subjects were followed for 6 months on ivacaftor in an open label trial.
- This is the largest study of participants taking ivacaftor with non-G551D gating mutations
- Participants experienced significant improvements in ppFEV₁, sweat chloride, and BMI.
- Positive responses in these endpoints were observed in pediatric and adult participants
- Pediatric subjects had higher baseline lung function and smaller improvement in ppFEV₁

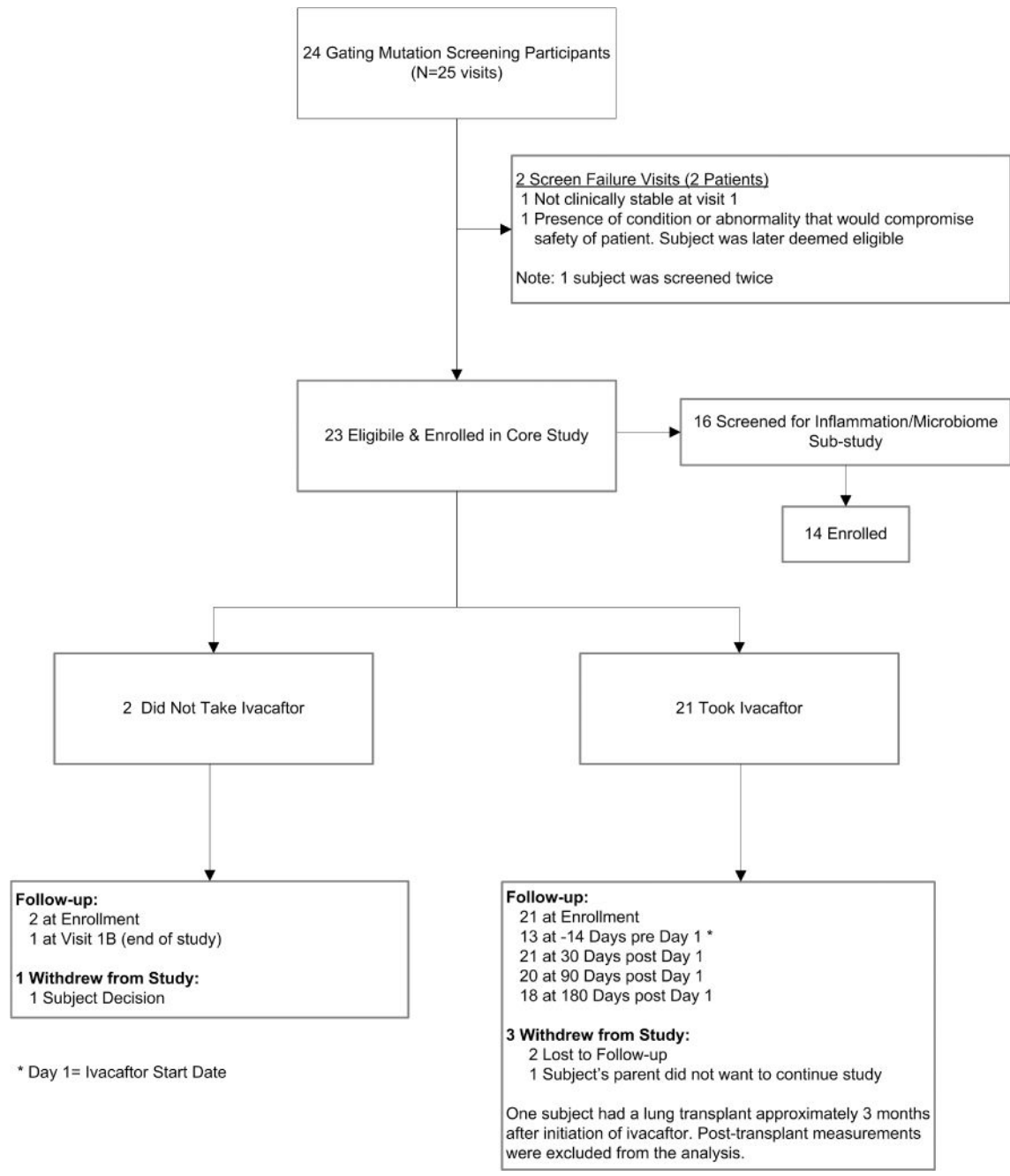


Figure 1.
Trial Consort Diagram

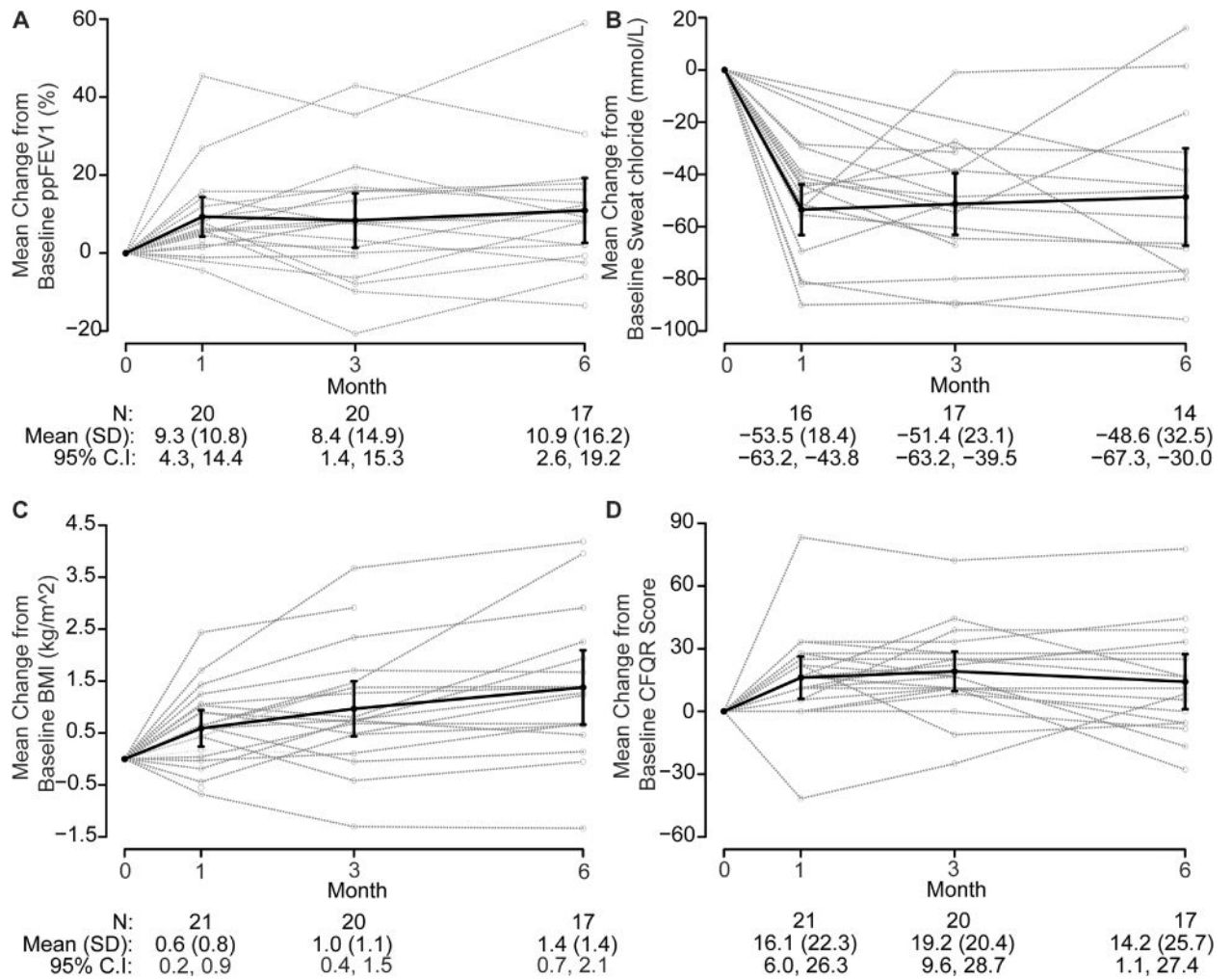


Figure 2. Mean change from baseline after 6 months of treatment
 (A) percent predicted FEV₁; (B) BMI; (C) sweat chloride; and (D) CFQR respiratory score.
 ppFEV₁ (percent predicted FEV₁); BMI (body mass index); CFQR-R (Cystic Fibrosis
 Questionnaire-Revised)

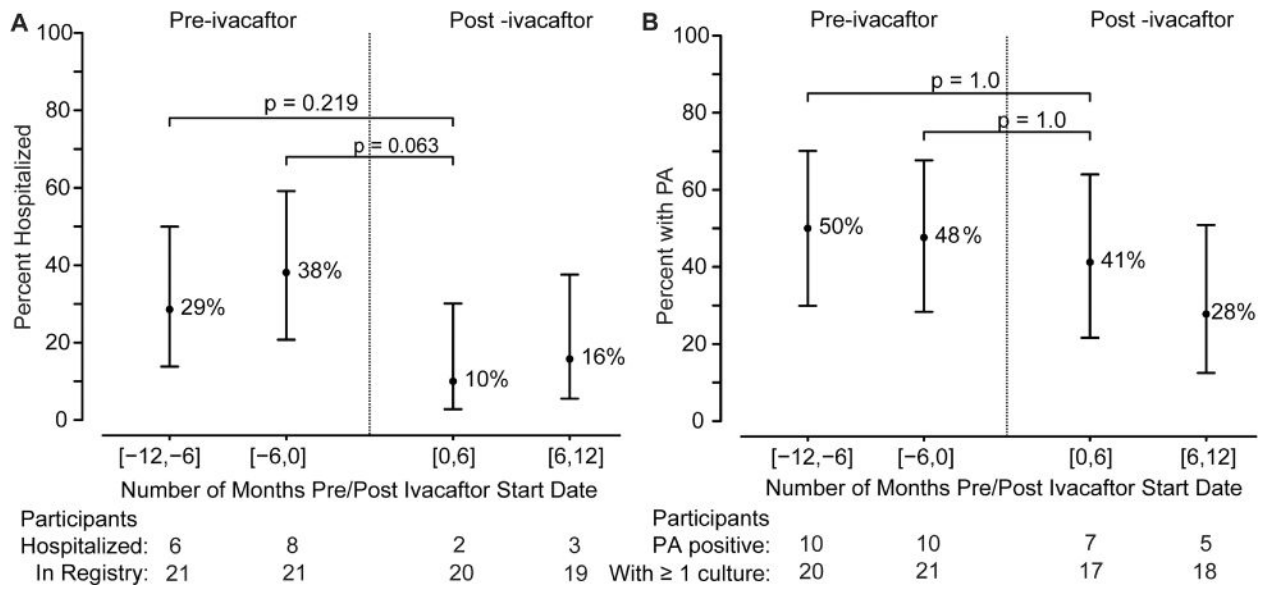


Figure 3. Hospitalization Rates and *P. Aeruginosa* Isolation

Data was extracted from CFF Patient Registry for the subjects in the time period 12 months before initiation of ivacaftor and in the time period after initiation of ivacaftor. (A) Percent of subjects hospitalized in the indicated time periods; (B) Percent of subjects with *P. Aeruginosa* (PA) in the indicated time period.

Table 1

Patient demographics.

Parameter	Subjects Taking Ivacaftor (N=21)	
Sex, n (%)	Female	9 (43%)
	Male	12 (57%)
Enrollment Age, mean (SD)		25.3 (16.2)
Enrollment Age, n (%)	6-11	4 (19%)
	12-17	7 (33%)
	18-29	4 (19%)
	30+	6 (29%)
Genotype, allele 1, n (%)	S549N	9 (42.8%)
	G178R	4 (19%)
	S1251N	4 (19%)
	S549R	2 (9.5%)
	S1255P	1 (4.8%)
	G551S	1 (4.8%)
Genotype, allele 2, n (%)	F508del	11 (52.4%)
	Unidentified	2 (9.5%)
	621+1G->T	1 (4.8%)
	S549R	1 (4.8%)
	3272-26A->C (RF)	1 (4.8%)
	L467P	1 (4.8%)
	Y913X	1 (4.8%)
	W1282X	1 (4.8%)
	711+3 A->G (RF)	1 (4.8%)
R352Q (RF)	1 (4.8%)	
Race, n (%)	Black/African-American	4 (19%)
	Hispanic	5 (24%)
	White	12 (57%)
FEV ₁ % Predicted, mean (SD)		68.0 (28.4)
FVC % Predicted, mean (SD)		81.2 (26.4)
BMI, mean (SD)		20.8 (4.2)

RF=residual function