

Manuscript Number: JCF-D-17-00110R1

Title: Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor

Article Type: Original Article

Keywords: Cystic fibrosis; Pulmonary exacerbations; Ivacaftor; Cystic fibrosis transmembrane conductance regulator; Pulmonary function

Corresponding Author: Dr. Patrick A. Flume, M.D.

Corresponding Author's Institution: Medical University of South Carolina

First Author: Patrick A. Flume, M.D.

Order of Authors: Patrick A. Flume, M.D.; Claire E Wainwright; D. Elizabeth Tullis; Sally Rodriguez; Minoo Niknian; Mark Higgins; Jane C Davies; Jeffrey S Wagener

Abstract: Background: Pulmonary exacerbations (PEx) are associated with acute loss of lung function that is often not recovered after treatment. We investigated lung function recovery following PEx for ivacaftor- and placebo-treated subjects.

Methods: Short- and long-term pulmonary function recovery data after PEx were summarized from a placebo-controlled trial in 161 cystic fibrosis patients ≥ 12 years old with the G551D-CFTR mutation (NCT00909532). Short-term recovery was measured 2 to 8 weeks after treatment, and long-term recovery was determined at the end-of-study, both compared with baseline measured just prior to the PEx.

Results: Fewer patients receiving ivacaftor experienced a PEx than patients receiving placebo (33.7% vs. 56.4%; $P = 0.004$) and had a lower adjusted incidence rate of PEx (0.589 vs. 1.382; $P < 0.001$). The proportion of PEx followed by full short-term recovery of percent predicted forced expiratory volume in 1 s was similar (ivacaftor vs. placebo, 57.1% vs. 53.7), as was the proportion of patients having long-term recovery (46.4% vs. 47.7%).

Conclusions: Ivacaftor treatment reduces the frequency of PEx but does not improve on the rate of complete lung function recovery after PEx when compared with placebo.

Highlights (3 to 5 bullet points, describing essence of research, limit 85 characters per bullet including spaces)

- Pulmonary exacerbations of cystic fibrosis associated with acute lung function loss
- Ivacaftor reduced pulmonary exacerbation frequency in patients with cystic fibrosis
- Lung function recovery post exacerbation similar between ivacaftor and placebo

April 6, 2017

Scott Bell, MD

Editor, *Journal of Cystic Fibrosis*

Dear Professor Bell,

We are pleased to submit for your consideration our manuscript, "*Recovery of Lung Function Following a Pulmonary Exacerbation in Patients With Cystic Fibrosis and the G551D-CFTR Mutation Treated With Ivacaftor*", for publication in the *Journal of Cystic Fibrosis*. I can confirm that this manuscript has been reviewed and approved by all the authors. The findings presented in this manuscript are not under consideration for publication elsewhere and have not been previously published in manuscript form.

In our manuscript we present post hoc analyses of short- and long-term recovery of pulmonary function following pulmonary exacerbations in patients enrolled in STRIVE, a placebo-controlled study of ivacaftor in patients with cystic fibrosis aged ≥ 12 years and at least one *G551D-CFTR* mutation. Our findings show that ivacaftor treatment reduced the likelihood and number of pulmonary exacerbations in these patients, but despite an overall treatment difference in pulmonary function vs placebo by the end of STRIVE, recovery of function following PEx was similar in ivacaftor- and placebo-treated patients.

While CFTR function with ivacaftor does improve long-term respiratory disease progression, our findings show that loss of lung function due to pulmonary exacerbation still occurs, and that prevention should remain a high priority for both treatment and future research. As such, we believe our manuscript will be of interest to your clinical readership as well as to cystic fibrosis researchers. We thank you for your time and consideration of our manuscript and look forward to your review.

Sincerely,

Patrick Flume, MD, on behalf of the authors

Reviewer #1:

The authors performed a post hoc analysis using data from an RCT of ivacaftor. Their objective was to determine if recovery of lung function differed between patients on ivacaftor compared with those on placebo. While exacerbations were far less frequent in patients randomized to ivacaftor, recovery of lung function was similar. This is a useful study to help elucidate some of the unknown complications of exacerbations in CF. It is generally a concise, well written paper, though I would like to see more information about how exacerbation treatment differed between the study arms. The authors indicate that fewer ivacaftor patients received IV antibiotics but the details are not entirely clear.

Response: *We appreciate the kind comments. As to the treatment of exacerbations, we agree that how patients were treated may influence outcomes, although we still do not have sufficient data to define optimal treatment options. Unfortunately, we lack complete details on how the patients' exacerbations were treated short of antibiotics and their method of delivery (i.e. oral vs. intravenous).*

Specific Comments:

1. In both the abstract and results section of the paper, the authors state that more in the ivacaftor group had no exacerbations. I would recommend they change the wording to state that fewer in the ivacaftor group had exacerbations.

Response: *We appreciate the suggestion and have made the recommended edits in the abstract, results, and discussion.*

2. In the abstract it would be helpful to very briefly define "short" and "long-term" pulmonary function recovery.

Response: *We have added brief definitions to the abstract as suggested.*

3. The authors use a definition of pulmonary exacerbation that includes treatment. While this is a common approach and may make the most sense in this study, the authors should discuss the potential shortcomings of this definition.

Response: *We appreciate the challenges of the definition of a PEx, which is why we used the most pragmatic one being the clinician decision to treat plus ≥ 4 signs or symptoms, which actually limits the diagnosis when compared with just using the decision to treat. We have included the following text in the discussion and hope this addresses the reviewer's comment to satisfaction:*

"For this analysis we used a pragmatic definition of a PEx. The combination of clinician decision to treat and the detection of multiple signs or symptoms has long been used in other reports of PEx (Fuchs et al, 1994). Although this definition is not a standardized one and there has long been an interest in deriving such a definition as it could standardize practice, the definition used in this analysis is consistent with clinical practice."

4. Long-term recovery could only be calculated once for patients with multiple exacerbations. While this makes sense, it would be worth commenting on whether the results look any different with these patients excluded.

Response: *We agree with the reviewer on this point. We conducted an analysis of long-term recovery in only those patients with exactly 1 PEx and presented these data in Table S2 in the*

supplement of the original manuscript (and cited on page 9 in the last paragraph of the results). There was no difference in the rate of recovery between placebo (9 of 21, 42.9%) and ivacaftor (6 of 15, 40.0%; $P=1.000$) among patients with exactly one PEx.

5. The results become confusing when trying to figure out the differences in use of IV antibiotics and hospitalization between the two study arms for patients with exacerbations. The text tries to clarify this, but it would be helpful to make this clearer in table 1.

Response: *We have added another footnote to Table 1 to clarify that IV antibiotics include both hospitalized events as well as those treated in the home setting.*

6. The primary results show the proportion that achieved complete recovery. It would also be nice to see the actual recovery of FEV1 in liters.

Response: *We appreciate the interest in even more data, however, the actual volume lost and recovered differs among patients in part because of their age, sex, and height. Further, given that this was a 12-month study, using actual FEV₁ data adds the complicating variable of patient growth over the study period, which could be different between the groups. While use of FEV₁ is a more sensitive variable, it is more appropriate in randomly-assigned studies of relatively short duration, to avoid the effect of changing height in younger patients.*

It is more common and understandable to normalize these measures using the percent of predicted, and we have provided some detail in Table S2. Although we have not given the change in lung function for each exacerbation, there is sufficient detail here to note that decline of lung function overall in the placebo group is consistent with other reports.

Reviewer #2: Overall, this is a well written manuscript presenting a post-hoc analysis of the phase 3 ivacaftor clinical trial focusing on recovery to baseline FEV1 after a pulmonary exacerbation. As pointed out by the authors, the data suggests that although ivacaftor treatment reduced the rate of PEx, the recovery of FEV1 after PEx for those who experienced one was not altered by this therapy. The paper is easy to follow and the data is clearly presented and has important clinical implications.

Response: *We appreciate the kind comments.*

Did the authors conduct a sensitivity analysis defining recovery of FEV1 as >90% baseline FEV1 - similar to the Sanders definition?

Response: *While we have conducted a number of sensitivity analyses for our manuscript (shown in Table S2), we only conducted analyses using recovery to 100% of function as our definition of recovery. The focus of the studies by Sanders et al was on risk factors for failure to recover. In our study, the interest was on successful recovery of function, and our clinical goal would be to restore full function to patients following a PEx. In addition, as we have noted in the conclusions, our findings on functional recovery were very similar to the Sanders et al studies, despite the differences in threshold for recovery. Further, there are recent (as yet unpublished) analyses of PEx recovery from the Epidemiological Study of Cystic Fibrosis (ESCF); although using 90%, 95%, and 100% thresholds for recovery of ppFEV₁ did show different numbers of patients with recovery of function after PEx, the overall trends were consistent between each threshold.*

My only minor comment is for the authors to consider framing the abstract conclusion a bit differently - rather than state that there are similar rates of lung function recovery between groups, consider stating that ivacaftor therapy does not improve the rate of complete recovery following PEx. This is an important distinction which leads to the implication that patients on ivacaftor who do have PEx need to be treated as aggressively as those who are not on a modulator, and that modulator therapy may reduce the occurrence of PEx but not their severity.

Response: *We appreciate the suggestion and have edited the abstract accordingly.*

Reference

Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 1994;331(10):637-42.

Title	Recovery of Lung Function Following a Pulmonary Exacerbation in Patients With Cystic Fibrosis and the G551D-CFTR Mutation Treated With Ivacaftor
Authors *Corresponding author	Patrick A. Flume, MD*; Claire E. Wainwright, MBBS, MD; D. Elizabeth Tullis, MD; Sally Rodriguez, MS; Minoo Niknian, PhD; Mark Higgins, MD; Jane C. Davies, MB ChB, MD; Jeffrey S. Wagener, MD
Corresponding author contact information	Patrick A. Flume, MD 96 Jonathan Lucas St Room 812-CSB, MSC 630 Charleston, SC 29425 USA Phone: 843-792-3167 E-mail: flumepa@musc.edu
Target journal	<i>Journal of Cystic Fibrosis</i>
Body word count (limit 3000)	2832
Abstract word count (limit 150)	154
Figures and tables (limit 5)	2 tables, 3 figures; 3 supplementary tables
References	27
Target submission date	TBD
Version	2

Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the *G551D-CFTR* mutation treated with ivacaftor

Running title: Lung function recovery after CF PEx with ivacaftor

Patrick A. Flume^{a,*}, Claire E. Wainwright^b, D. Elizabeth Tullis^c, Sally Rodriguez^d, Minoo Niknian^e, Mark Higgins^f, Jane C. Davies^g, Jeffrey S. Wagener^h

^aDepartments of Medicine and Pediatrics, Medical University of South Carolina, 96 Jonathan Lucas St, Room 812-CSB, MSC 630, Charleston, SC 29425, USA

^bUniversity of Queensland, Level 7, Centre for Child Health Research, Graham St, South Brisbane, Queensland 4101, Australia and the Lady Cilento Children's Hospital, 501 Stanley St, South Brisbane , Australia 4101.

^c Division of Respiriology and Keenan Research Centre of Li Ka Shing Knowledge Institute, Department of Medicine, St. Michael's Hospital, University of Toronto, 1 King's College Circle, 6263 Medical Sciences Building, Toronto, ON M5S 1A8, Canada

^dJohnson & Johnson Medical Devices, 325 Paramount Dr, Raynham, MA 02767, USA

^eVertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210, USA

^fVertex Pharmaceuticals (Europe) Limited, 86-88 Jubilee Avenue, Milton Park, Abingdon, Oxfordshire OX14 4RW, UK

^gNational Heart and Lung Institute, Imperial College, London, UK and Department of Pediatric Respiratory Medicine, Royal Brompton and Harefield National Health Service Foundation Trust, Sydney Street, London, SW3 6NP, UK

^hDepartment of Pediatrics, University of Colorado School of Medicine, 13123 E 16th Ave, Aurora, CO 80045, USA

Author emails: flumepa@musc.edu (P.A. Flume), claire.wainwright@health.qld.gov.au (C.E. Wainwright), tullis@smh.ca (D.E. Tullis), srodr127@its.jnj.com (S. Rodriguez), minoo_niknian@vrtx.com (M. Niknian), mark_higgins@vrtx.com (M. Higgins), j.c.davies@imperial.ac.uk (J.C. Davies), jeffrey.wagener@ucdenver.edu (J.S. Wagener)

*Corresponding author at: Departments of Medicine and Pediatrics, Medical University of South Carolina, 96 Jonathan Lucas St, Room 812-CSB, MSC 630, Charleston, SC 29425 USA. Tel: +1 843-792-3167
E-mail address: flumepa@musc.edu (P.A. Flume)

Presented at the 36th European Cystic Fibrosis Society (ECFS) Conference, Lisbon, Portugal, 12-15 June 2013.

Abstract (154 Words/Limit 150)

Background: Pulmonary exacerbations (PE_x) are associated with acute loss of lung function that is often not recovered after treatment. We investigated lung function recovery following PE_x for ivacaftor- and placebo-treated subjects.

Methods: Short- and long-term pulmonary function recovery data after PE_x were summarized from a placebo-controlled trial in 161 cystic fibrosis patients ≥12 years old with the G551D-

CFTR mutation (NCT00909532). Short-term recovery was measured 2 to 8 weeks after treatment, and long-term recovery was determined at the end-of-study, both compared with baseline measured just prior to the PE_x.

Results: ~~Fewer P~~patients receiving ivacaftor ~~were more likely to~~ experienced ~~a~~ PE_x than patients receiving placebo (33.766.3% vs. 56.443.6%; $P = 0.004$) and had a lower adjusted incidence rate of PE_x (0.589 vs. 1.382; $P < 0.001$). The proportion of PE_x followed by full short-term recovery of percent predicted forced expiratory volume in 1 s was similar (ivacaftor vs. placebo, 57.1% vs. 53.7), as was the proportion of patients having long-term recovery (46.4% vs. 47.7%).

Conclusions: Ivacaftor treatment reduces the frequency of PE_x, but does not improve on the rate of both arms had similar rates of complete lung function recovery after PE_x when compared with placebo.

Keywords: Cystic fibrosis; Pulmonary exacerbations; Ivacaftor; Cystic fibrosis transmembrane conductance regulator; Pulmonary function

1. Introduction

Pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF) are associated with a more rapid decline in lung function [1], poorer quality of life [2], increased healthcare costs [3], and early mortality [4, 5]. Although no standardized definition exists [6, 7], in general a PEx is considered to have occurred when a patient presents with increased signs and symptoms of respiratory tract illness, and the clinician decides to begin (or make changes to existing) antibiotic treatment. Avoiding PEx is a key therapeutic goal. When a PEx does occur, loss of lung function frequently occurs [8], and one goal of treatment is to recover this lost function. However, even following treatment and clinical improvement, recovery of lung function is often incomplete [8-13] and accounts for half of the long-term lung function decline in patients with CF [8].

Several factors may contribute to this unrecovered loss of lung function. Although the underlying factors associated with PEx are not always clear, some causes may be more harmful and difficult to treat than others. For example, patients with *Pseudomonas aeruginosa* infection have greater airway inflammation than patients with other bacterial infections and, theoretically, will experience greater airway damage over time [14]. A second factor contributing to PEx-related loss of lung function may be the treatment, either because it is insufficient or delayed; hence, prevention of PEx becomes a key aspect of chronic management. Although antibiotics are almost universally prescribed for PEx, there are no standard approaches for the choice and duration of antibiotic therapy [13, 15]. Finally, host factors, including severity of lung disease, nutritional status, comorbidities, and the use of chronic therapies, may contribute to the impact of PEx. Baseline lung function and the extent of lung function loss associated with PEx may influence the choice of treatment and independently impact the likelihood of recovery [13, 16].

Ivacaftor is a CF transmembrane conductance regulator (CFTR) protein potentiator approved for the treatment of patients with CF who have at least one gating mutation (e.g., *G551D-CFTR*). Ivacaftor targets the underlying disease mechanism in CF, potentiating the

function of the CFTR protein to increase chloride ion secretion in bronchial (and other) epithelial cells, and thereby reducing excess fluid absorption and increasing ciliary beating [17]. In clinical experience, patients receiving ivacaftor have demonstrated improved lung function, improved mucociliary clearance, and lower sputum culture positivity for *P. aeruginosa* [18]. It is plausible that the improvement in mucociliary clearance observed in patients following ivacaftor treatment may enhance the clearance of infective bacteria and inflammatory material following a PEx event, and in so doing also allow for improvement in recovery of lung function after such an event. A placebo-controlled clinical study of ivacaftor in patients with CF ≥ 12 years old (STRIVE) [19] was of sufficient duration to assess the impact of PEx on lung function. We designed this post hoc analysis to assess lung function recovery following a PEx for ivacaftor- and placebo-treated patients.

2. Methods

Data from patients enrolled in the STRIVE clinical study were used in this analysis (NCT00909532). Methods and results for this study were previously reported [19]. STRIVE included 161 patients with CF who had at least one *G551D-CFTR* gene mutation and were ≥ 12 years old, with a baseline percent predicted forced expiratory volume in 1 s (ppFEV₁) of 40 to 90. Patients could not have been treated for PEx in the 4 weeks prior to enrollment. This study lasted 48 weeks, and patients were examined and underwent pulmonary function testing at baseline and at study weeks 2, 8, 16, 24, 32, 40, and 48. Thus, values closest to the PEx were used for analysis. Local ethics committees approved the original protocols, and all patients provided written informed consent or assent, as appropriate.

A PEx was defined a priori as any clinician-determined new or changed antibiotic therapy (intravenous [IV], inhaled, or oral) for four or more protocol-defined signs or symptoms as used by Fuchs et al. [20]. Antibiotic start and stop dates were recorded and were at the clinician's discretion. For analyses of event rates, *P* values were derived from negative binomial

1
2
3
4 regressions that included number of events as the dependent variable, treatment as a fixed
5
6 effect, adjustments for baseline ppFEV₁ severity (<70 vs. ≥70), and age group (<18 years vs.
7
8 ≥18 years), with log (time on study) as an offset. Regressions were only conducted when the
9
10 number of patients with events in each treatment group was five or more and when the model
11
12 converged; otherwise, *P* values were derived from Fisher's exact test on the number of patients
13
14 with events. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary,
15
16 NC, USA).
17

18
19
20 Lung function recovery following PEx was defined as a return to at least 100% of the
21
22 pre-exacerbation ppFEV₁ measurement. Important for this analysis was the lack of pulmonary
23
24 function testing immediately prior to or at the end of a PEx. In order to be included in the lung
25
26 function analysis, patients had to have spirometry results obtained during study visits both
27
28 before and after a PEx; multiple PEx occurring between spirometry measurements were treated
29
30 as one event for the purposes of lung function recovery analyses. Short-term recovery was
31
32 calculated for each PEx by comparing the most recent pre-exacerbation ppFEV₁ with that
33
34 measured 2 to 8 weeks after stopping the new or changed antibiotic. Long-term recovery was
35
36 determined by the change in ppFEV₁ from the pre-exacerbation value to the end-of-study value
37
38 (duration varied depending on when during the study the PEx occurred). Long-term recovery
39
40 was calculated only once (using the first PEx) for patients with more than one PEx. Lung
41
42 function recovery data were also summarized according to the number of observed PEx events
43
44 and from patients treated with IV antibiotics, whether or not they met the a priori criteria for a
45
46 PEx.
47
48
49
50
51
52

53 **3. Results**

54
55 Baseline demographics demonstrated that the 83 ivacaftor- and 78 placebo-treated
56
57 patients were well matched for age, sex, nutritional status, ppFEV₁ (mean ± SD, 63.5 ± 16.1 vs.
58
59 63.7 ± 16.8), and sweat chloride [19].
60
61
62
63
64
65

Overall, ~~more~~ fewer patients in the ivacaftor group had ~~no~~ PEx events reported during the study period (n = ~~2855~~ 33.766.3%) than in the placebo group (n = ~~4434~~ 56.443.6%; $P = 0.004$), and more patients in the placebo group experienced three or more PEx (n = 14 [17.9%]) than the ivacaftor group (n = 4 [4.8%]; $P = 0.01$; Fig. 1). The rate of pulmonary exacerbations (1.382 and 0.589 for placebo and ivacaftor, respectively) was 57.4% lower in the ivacaftor group than in the placebo group (rate ratio [95% confidence interval (CI)], 0.426 [0.268–0.676]; $P < 0.001$; Table 1) and the rate of sinopulmonary signs and symptoms (2.577 and 1.477 for placebo and ivacaftor, respectively) was 42.7% lower in the ivacaftor group than in the placebo group (rate ratio [95% CI], 0.573 [0.423–0.776]; $P < 0.001$). The frequency of specific signs and symptoms that were associated with PEx events in patients receiving ivacaftor and placebo are shown in Table 2. Overall, increased cough was the most frequently reported symptom, with the other most common symptoms being a change in sputum, malaise/fatigue/lethargy, and increased dyspnea.

The mean number of days with PEx per patient (normalized for time on study) in the ivacaftor group was significantly less than in the placebo group (mean normalized days with PEx per patient, 13.5 vs. 36.7; $P < 0.001$; Table 1). Of the 146 PEx events recorded during the study (99 in the placebo group and 47 in the ivacaftor group), 75 (51.4%) were treated with IV antibiotics, and 52 (35.6%) were treated by inpatient hospitalization. As shown in Table 1, the proportion of patients with PEx treated with IV antibiotics and the proportion undergoing hospitalization were greater in the placebo group than the ivacaftor group ($P = 0.02$ and $P = 0.01$, respectively); no significant difference in events treated by hospitalization was detected ($P = 0.19$). Additionally, considering all patients in both treatment groups, the mean duration of IV antibiotic therapy for PEx (normalized for time on study) was shorter in the ivacaftor group than in the placebo group ($P = 0.02$; Table 1).

As noted above, more patients in the placebo group (n=44) experienced ≥ 1 PEx during the study than in the ivacaftor group (n=28). For those patients experiencing ≥ 1 PEx,

demographics and baseline characteristics were well-balanced for age, sex, nutritional status, ppFEV₁, and sweat chloride; mean ppFEV₁ preceding the first PEx was higher in the ivacaftor group (Table S1).

The proportion of patients with complete (i.e., ≥100%) long-term ppFEV₁ recovery was similar in the ivacaftor and placebo groups (46.4% vs. 47.7%; Fig. 2A). For the short-term recovery analysis, multiple PEx occurring between two spirometry assessments were collapsed into single events, such that there were 54 qualifying events in the placebo group and 28 in the ivacaftor group. The proportion of these events followed by complete short-term ppFEV₁ recovery was similar in the ivacaftor and placebo groups (57.1% vs. 53.7%; Fig. 2B).

In the analyses described above we included all PEx, including those treated with IV and oral antibiotics. To investigate the impact of antibiotic treatment on recovery from PEx we performed additional analyses comparing the groups based on all patients treated with IV antibiotics specifically for a PEx, all patients treated with any antibiotic (i.e., they did not meet the full criteria of a PEx), and all patients with one or more sign or symptom treated with IV antibiotics. We found no differences in long-term recovery of lung function between the groups in any of these comparisons (Table S2). As patients in the placebo group were more likely to experience more than one PEx than those in the ivacaftor group, we also looked for differences in rates of lung function recovery between the groups using only those patients with just one PEx, but found none (Table S2). By the end of 48 weeks, patients who received ivacaftor and had multiple PEx experienced benefits in ppFEV₁ (Figure 3) and other spirometric measures of lung function (Table S3), as did patients who received ivacaftor and had no PEx, whereas patients who received placebo had near-baseline or a decline in lung function, regardless of the number of PEx.

4. Discussion

In this post hoc analysis of a placebo-controlled study, patients ≥ 12 years old with CF and a *G551D-CFTR* gene mutation who were treated with ivacaftor had a reduced frequency of PEx, ~~and~~ were ~~more~~ less likely to experience ~~any~~ PEx, and less likely to experience three or more PEx during the study period than patients treated with placebo. Further, a smaller proportion of patients receiving ivacaftor experienced PEx treated with IV antibiotics and a smaller proportion underwent inpatient hospitalization than patients receiving placebo. Overall, patients in the ivacaftor group demonstrated substantial lung function improvement regardless of PEx incidence, but there was no apparent difference (vs. placebo) in the likelihood to recover function fully after a PEx.

For this analysis, we defined lung function recovery as a return to at least 100% of the patient's pre-exacerbation ppFEV₁, whereas other studies have used different standards for recovery. Sanders et al. [12] defined a responder as achieving 95% of baseline FEV₁ within 3 months of ending a hospitalization for a PEx and found that 23% of children did not recover. When they looked for 100% recovery to baseline, 42.3% of patients did not achieve this goal. Our finding that 46.3% and 42.9% of patients in the placebo and ivacaftor groups, respectively, did not recover to 100% of their pre-exacerbation FEV₁ by 2 to 8 weeks following a PEx is strikingly similar, although our analysis did not require hospitalization and included both IV and oral antibiotic-treated patients. This lack of recovery among both IV and oral antibiotic-treated patients is consistent with epidemiologic findings showing that both short-term and long-term loss of lung function occurs regardless of the choice of antibiotics [13].

In a subsequent study by Sanders et al. using US Cystic Fibrosis Foundation Patient Registry data (for patients aged ≥ 6 years) and defining recovery as 90% of baseline lung function [21], 25% of patients failed to recover within 3 months of a hospitalization for a PEx. Furthermore, 58% of these patients who failed to recover still had not recovered to 90% of

1
2
3
4 baseline function by 1 year following the PEx. Again, the results of our post hoc analysis are
5
6 similar: there were patients in both the ivacaftor (53.6%) and placebo (52.3%) groups who failed
7
8 to achieve their pre-exacerbation lung function by the end of 48 weeks. However, in the present
9
10 study our goal was 100% of pre-exacerbation lung function, and we included all patients in our
11
12 48-week analysis, whereas in Sanders et al. [21], patients who recovered to 90% function by 3
13
14 months after PEx were excluded from the 6- and 12-month analyses. It should be noted that our
15
16 definition of long-term recovery as a return to $\geq 100\%$ of the pre-exacerbation FEV₁ value does
17
18 not account for potential lung function decline that can occur independently of PEx in the
19
20 context of CF as a progressive disease.
21
22

23
24 The strength of our analysis is that these data were captured during a placebo-controlled
25
26 trial with scheduled visits, whereas previous studies have typically used registry data obtained
27
28 during usual clinical care. However, this study was not specifically designed to address changes
29
30 in the severity or nature of PEx or time to lung function recovery after PEx. Additionally, patients
31
32 described here were initially assessed during a period of stability, establishing a true baseline
33
34 for lung function rather than using the highest recorded value in the registry as the patient's
35
36 baseline. Since patients often experience an acute increase in lung function with ivacaftor
37
38 treatment, we based our recovery calculation on the FEV₁ immediately prior to a PEx, with the
39
40 assumption that this newer, often higher value was their new baseline. Finally, so that these
41
42 results (using a protocol-defined definition of a PEx) can be compared with results from
43
44 epidemiologic studies, we looked at multiple subsets of patients; we saw similar results when
45
46 we analyzed data restricted to patients who were treated with IV antibiotics.
47
48
49
50

51 A recent study of long-term ivacaftor use has shown a reduction in the rate of decline of
52
53 lung function [22], suggesting that CFTR modulation modifies disease progression. Our results
54
55 demonstrate that the adverse outcomes attributed to PEx (i.e., loss of lung function) occur even
56
57 when addressing the underlying cause of CF and improving CFTR function in the host (though
58
59 not to the level of function of wild-type CFTR [17]). Since no therapy has proven to be effective
60
61
62
63
64
65

1
2
3
4 in reversing lung function loss following a PEx, prevention should be a high priority. Indeed,
5
6 ivacaftor has been shown to reduce the incidence of PEx both in clinical trials [19] and in the
7
8 setting of real-world clinical practice [23]. It may be noted that multiple studies of therapies
9
10 directed at airway disease in CF such as hypertonic saline and the antibiotics azithromycin and
11
12 inhaled tobramycin have shown a reduction in PEx frequency; however, those studies did not
13
14 assess the therapeutic impact on recovery [24-26].
15
16

17
18 Collectively, these data suggest that altering host tissue physiology by modifying CFTR
19
20 function with ivacaftor does not prevent the adverse impact of PEx on lung function.
21

22 Nonetheless, in patients treated with ivacaftor who had one or more PEx, there was a large
23
24 improvement in ppFEV₁ at the end of the study compared with their original baseline, whereas
25
26 in patients receiving placebo there was no improvement. This suggests that the change in
27
28 CFTR function produced by ivacaftor may affect patients in a way that results in long-term
29
30 disease modification but does not affect the way lung tissue responds to acute PEx and their
31
32 treatment. One can theorize in terms of mechanism that the long-term benefits of improved
33
34 mucociliary clearance may be overwhelmed by airway injury during a PEx.
35
36

37
38 For this analysis we used a pragmatic definition of a PEx. The combination of clinician
39
40 decision to treat and the detection of multiple signs or symptoms has long been used in other
41
42 reports of PEx [20]. Although this definition is not a standardized one and there has long been
43
44 an interest in deriving such a definition as it could standardize practice, the definition used in
45
46 this analysis is consistent with clinical practice. An important limitation of the present analysis is
47
48 that the STRIVE clinical study was not designed to assess lung function recovery outcomes
49
50 following PEx. Assessment of short- and long-term recovery from PEx represents a post hoc
51
52 analysis in which the subgroups (those with PEx) were outcomes related to treatment allocation,
53
54 such that the patients who received ivacaftor and had PEx may be different to those who
55
56 received placebo and had PEx. Therefore the findings should be considered exploratory and
57
58 interpreted with caution. It should also be noted that specific information was not collected
59
60
61
62
63
64
65

1
2
3
4 during the STRIVE study regarding the etiology underlying PEx events, the specific antibiotics
5 used, or the utilization of other PEx treatments. Additionally, microbiology data were only
6 available at baseline, and no FEV₁ measurements during the PEx were recorded.
7
8
9

10
11 In conclusion, patients aged ≥12 years old with CF and a *G551D-CFTR* gene mutation
12 receiving ivacaftor were less likely to experience any PEx and experienced fewer PEx events
13 versus those receiving placebo. However, the proportion of patients with complete lung function
14 recovery in the short term and long term following a PEx was similar in the ivacaftor and
15 placebo groups. This finding suggests that addressing the underlying cause of CF disease by
16 altering CFTR protein function does reduce the incidence and duration of PEx and improve
17 long-term lung health, even when PEx do occur, but appears to have no measurable effect on
18 the likelihood of 100% recovery of pre-exacerbation lung function following a PEx.
19
20
21
22
23
24
25
26
27
28
29
30

31 **Funding**

32
33 This study was sponsored by Vertex Pharmaceutical Incorporated.
34

35 P.A. Flume's research time was supported by the South Carolina Clinical & Translational
36 Research (SCTR) Institute, with an academic home at the Medical University of South Carolina,
37 through NIH grant number UL1 TR001450. D.E. Tullis' research time was supported by the
38 Cystic Fibrosis Canada Chair in Adult CF Research. J.C. Davies' research time was supported
39 by the National Institute of Health Research, Respiratory Biomedical Research Unit at the Royal
40 Brompton and Harefield, NHS Foundation Trust and Imperial College, London.
41
42
43
44
45
46
47
48
49
50

51 **Conflict of interest**

52
53 M. Niknian and M. Higgins are employees of Vertex Pharmaceuticals Incorporated and may
54 own stock or stock options in that company. J.S. Wagener and S. Rodriguez were previously
55 employed by Vertex Pharmaceuticals Incorporated and may own stock or stock options in that
56 company. P.A. Flume, C.E. Wainwright, D.E. Tullis, J.C. Davies, and J.S. Wagener have
57
58
59
60
61
62
63
64
65

1
2
3
4 consulted for, and their institutions have received research funding from, Vertex
5
6 Pharmaceuticals Incorporated.
7
8
9

10 **Author contributions**

11
12 P.A. Flume, S. Rodriguez, and J.S. Wagener contributed to the study design. All authors
13 participated in data analysis/interpretation and critical review and revision of the manuscript.
14
15 P.A. Flume and J.S. Wagener participated in project management. S. Rodriguez, M. Niknian,
16
17 and J.S. Wagener participated in data management and statistical analysis. All authors
18
19 approved the final draft for submission.
20
21
22
23
24
25

26 **Acknowledgments**

27
28 We thank the patients and their families who participated in the clinical study, as well as
29
30 Elizabeth Dorn, PhD, and Dhrupad Patel, PharmD, from Vertex Pharmaceuticals Incorporated,
31
32 who assisted with manuscript preparation, and Bonnie Bielefeld, MS, an employee of
33
34 BioBridges, for statistical programming and data review support. Medical writing and editorial
35
36 support were provided by Jeremy Kennard, PhD, Dena McWain, and Shannon Davis of Ashfield
37
38 Healthcare Communications, which received funding from Vertex Pharmaceuticals
39
40 Incorporated.
41
42
43
44
45

46 **Supplementary data to this article can be found online at XXXX.**

47
48 Data includes:
49

50
51 Table S1. Demographics, baseline characteristics, and ppFEV₁ preceding first PEx for patients
52
53 who had ≥1 PEx during study
54

55
56 Table S2. Proportion of patients with full (≥100%) recovery of lung function following treatment
57
58 of protocol-defined PEx
59

60
61 Table S3. Change from baseline in spirometry measures at week 48
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References

- [1] Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* 2007;151(2):134-9, 9 e1.
- [2] Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002;121(1):64-72.
- [3] Lieu TA, Ray GT, Farmer G, Shay GF. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics* 1999;103(6):e72.
- [4] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;153(4):345-52.
- [5] Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *Am J Respir Crit Care Med* 2002;166(12 Pt 1):1550-5.
- [6] Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. *J Pediatr* 2006;148(2):259-64.
- [7] Bilton D, Canny G, Conway S, Dumcius S, Hjelte L, Proesmans M, et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. *J Cyst Fibros* 2011;10(Suppl 2):S79-81.
- [8] Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* 2012;40(1):61-6.
- [9] Collaco JM, Green DM, Cutting GR, Naughton KM, Mogayzel PJ, Jr. Location and duration of treatment of cystic fibrosis respiratory exacerbations do not affect outcomes. *Am J Respir Crit Care Med* 2010;182(9):1137-43.

- 1
2
3
4 [10] Heltshe SL, Goss CH, Thompson V, Sagel SD, Sanders DB, Marshall BC, et al. Short-
5
6 term and long-term response to pulmonary exacerbation treatment in cystic fibrosis. Thorax
7
8 2015;71(3):223-9.
9
- 10 [11] Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations
11
12 are associated with subsequent FEV₁ decline in both adults and children with cystic fibrosis.
13
14 Pediatr Pulmonol 2011;46(4):393-400.
15
- 16 [12] Sanders DB, Hoffman LR, Emerson J, Gibson RL, Rosenfeld M, Redding GJ, et al.
17
18 Return of FEV₁ after pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol
19
20 2010;45(2):127-34.
21
22
- 23 [13] Wagener JS, Rasouliyan L, VanDevanter DR, Pasta DJ, Regelman WE, Morgan WJ, et
24
25 al. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic
26
27 fibrosis. Pediatr Pulmonol 2013;48(7):666-73.
28
29
- 30 [14] Sagel SD, Gibson RL, Emerson J, McNamara S, Burns JL, Wagener JS, et al. Impact of
31
32 Pseudomonas and Staphylococcus infection on inflammation and clinical status in young
33
34 children with cystic fibrosis. J Pediatr 2009;154(2):183-8.
35
36
- 37 [15] Flume PA, Mogayzel PJ, Robinson KA, Goss CH, Rosenblatt R, Kuhn R, et al. Cystic
38
39 Fibrosis Pulmonary Guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care
40
41 Med 2009;180(9):802-8.
42
43
- 44 [16] Morgan WJ, Wagener JS, Yegin A, Pasta DJ, Millar SJ, Konstan MW, et al. Probability
45
46 of treatment following acute decline in lung function in children with cystic fibrosis is related to
47
48 baseline pulmonary function. J Pediatr 2013;163(4):1152-7 e2.
49
50
- 51 [17] Van Goor F, Hadida S, Grootenhuys PD, Burton B, Cao D, Neuberger T, et al. Rescue of
52
53 CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S
54
55 A 2009;106(44):18825-30.
56
57
58
59
60
61
62
63
64
65

- [18] Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. *Am J Respir Crit Care Med* 2014;190(2):175-84.
- [19] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365(18):1663-72.
- [20] Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. [The Pulmozyme Study Group \[comment\]](#). *N Engl J Med* 1994;331(10):637-42.
- [21] Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010;182(5):627-32.
- [22] Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med* 2015;192(7):836-42.
- [23] Hassan M, Bonafede MM, Limone BL, Hodgkins P, Suthoff ED, Sawicki G. Reduction in pulmonary exacerbations (PEX) after initiation of ivacaftor: a retrospective cohort study among patients with cystic fibrosis (CF) treated in real-world settings. *J Cyst Fibros* 2016;15(Suppl 1):S58.
- [24] Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354(3):229-40.
- [25] Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;340(1):23-30.

- 1
2
3
4 [26] Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al.
5
6 Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*:
7
8 a randomized controlled trial. JAMA 2003;290(13):1749-56.
9
10
11 [27] VanDevanter DR, Flume PA, Morris N, Konstan MW. Probability of IV antibiotic
12
13 retreatment within thirty days is associated with duration and location of IV antibiotic treatment
14
15 for pulmonary exacerbation in cystic fibrosis. J Cyst Fibros 2016;15(6):783-90
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

TABLES

Table 1

Protocol-defined PEx over a 48-week period.

PEx event	Placebo (n = 78)	Ivacaftor (n = 83)	<i>P</i> value ^a
Patients with events, n (%)	44 (56.4)	28 (33.7)	0.004
Number of events, n (event rate) ^b	99 (1.382)	47 (0.589)	<0.001 ^c
Normalized days per patient with events, mean ± SD ^d	36.67 ± 49.537	13.54 ± 27.269	<0.001 ^e
Number of patients treated with IV antibiotics for PEx, n (%) ^f	27 (34.6)	15 (18.1)	0.02
Normalized days per patient of IV antibiotic therapy for PEx, mean ± SD ^{d,f}	11.03 ± 20.355	6.68 ± 19.429	0.02 ^e
Number of events treated with IV antibiotic therapy, n (event rate) ^{e,b,f}	47 (0.711)	28 (0.397)	0.08 ^c
Number of patients undergoing hospitalization for PEx, n (%)	23 (29.5)	11 (13.3)	0.01
Number of events treated by hospitalization, n (event rate) ^b	31 (0.489)	21 (0.311)	0.19 ^c

^aUnless otherwise stated (^{c, e}), *P* values are from Fisher's exact test.

^bEstimates of event rates were obtained from negative binomial regression with the number of events as the dependent variable, treatment as a fixed effect, and adjustment for baseline ppFEV₁ severity (<70 vs ≥70), and age group (<18 vs ≥18 years), with log (time on study) as an offset.

^c*P* values are from the treatment effect in negative binomial regression.

^dNormalized days are defined as days with events adjusted for time spent in the study by multiplying the observed proportion of days with events by the total study days expected (i.e., 336 days for 48 weeks).

^e*P* values are from a stratified (by baseline ppFEV₁ severity and age group) Wilcoxon rank-sum test.

^f[The use of IV antibiotics includes events treated at home or in hospital.](#)

IV, intravenous; PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s; SD, standard deviation.

Table 2

Signs and symptoms reported in patients who experienced a protocol-defined PEx

	Placebo (n = 44) [99 events]	Ivacaftor (n = 28) [47 events]
Clinical sign or symptom	n (%)	n (%)
Increased cough	95 (96.0)	46 (97.9)
Change in sputum	83 (83.8)	40 (85.1)
Malaise, fatigue, or lethargy	62 (62.6)	38 (80.9)
Increased dyspnea	55 (55.6)	27 (57.4)
Chest examination (change)	34 (34.3)	19 (40.4)
10% drop in FEV ₁	31 (31.3)	11 (23.4)
Sinus discharge (change)	29 (29.3)	12 (25.5)
Temperature >38°C	20 (20.2)	12 (25.5)
Sinus pain or tenderness	19 (19.2)	11 (23.4)
Anorexia or weight loss	21 (21.2)	8 (17.0)
Hemoptysis (new or increased)	13 (13.1)	10 (21.3)
Radiographic changes of new pulmonary infection	10 (10.1)	1 (2.1)

FEV₁, forced expiratory volume in 1 s; PEx, pulmonary exacerbation.

FIGURES

Fig. 1. Percentage of patients in the STRIVE study by number of protocol-defined PEx. PEx, pulmonary exacerbations.

Fig. 2. Proportion of patients experiencing protocol-defined PEx with full long-term functional recovery (A) and proportion of protocol-defined PEx events followed by full short-term functional recovery (B). Long-term recovery is defined as the return to $\geq 100\%$ of pre-exacerbation ppFEV₁ at end of study participation (week 48 or last on-treatment visit; shown as proportion of total number of patients experiencing PEx, panel A). Short-term recovery is defined as the return to $\geq 100\%$ of pre-PEx ppFEV₁ within 2 to 8 weeks after event (shown as proportion of total PEx events, panel B).

PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s.

Fig. 3. Improvement from study baseline in ppFEV₁ at week 48 by number of protocol-defined PEx. Data are shown for patients with non-missing FEV₁ measurements at week 48. FEV₁, forced expiratory volume in 1 s; PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s.

Title	Recovery of Lung Function Following a Pulmonary Exacerbation in Patients With Cystic Fibrosis and the G551D-CFTR Mutation Treated With Ivacaftor
Authors *Corresponding author	Patrick A. Flume, MD*; Claire E. Wainwright, MBBS, MD; D. Elizabeth Tullis, MD; Sally Rodriguez, MS; Minoo Niknian, PhD; Mark Higgins, MD; Jane C. Davies, MB ChB, MD; Jeffrey S. Wagener, MD
Corresponding author contact information	Patrick A. Flume, MD 96 Jonathan Lucas St Room 812-CSB, MSC 630 Charleston, SC 29425 USA Phone: 843-792-3167 E-mail: flumepa@musc.edu
Target journal	<i>Journal of Cystic Fibrosis</i>
Body word count (limit 3000)	2832
Abstract word count (limit 150)	154
Figures and tables (limit 5)	2 tables, 3 figures; 3 supplementary tables
References	27
Target submission date	TBD
Version	2

Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the *G551D-CFTR* mutation treated with ivacaftor

Running title: Lung function recovery after CF PEx with ivacaftor

Patrick A. Flume^{a,*}, Claire E. Wainwright^b, D. Elizabeth Tullis^c, Sally Rodriguez^d, Minoo Niknian^e, Mark Higgins^f, Jane C. Davies^g, Jeffrey S. Wagener^h

^aDepartments of Medicine and Pediatrics, Medical University of South Carolina,
96 Jonathan Lucas St, Room 812-CSB, MSC 630, Charleston, SC 29425, USA

^bUniversity of Queensland, Level 7, Centre for Child Health Research, Graham St, South
Brisbane, Queensland 4101, Australia and the Lady Cilento Children's Hospital, 501 Stanley St,
South Brisbane , Australia 4101.

^c Division of Respiriology and Keenan Research Centre of Li Ka Shing Knowledge Institute,
Department of Medicine, St. Michael's Hospital, University of Toronto, 1 King's College Circle,
6263 Medical Sciences Building, Toronto, ON M5S 1A8, Canada

^dJohnson & Johnson Medical Devices, 325 Paramount Dr, Raynham, MA 02767, USA

^eVertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210, USA

^fVertex Pharmaceuticals (Europe) Limited, 86-88 Jubilee Avenue, Milton Park, Abingdon,
Oxfordshire OX14 4RW, UK

^gNational Heart and Lung Institute, Imperial College, London, UK and Department of Pediatric
Respiratory Medicine, Royal Brompton and Harefield National Health Service Foundation Trust,
Sydney Street, London, SW3 6NP, UK

^hDepartment of Pediatrics, University of Colorado School of Medicine, 13123 E 16th Ave,
Aurora, CO 80045, USA

Author emails: flumepa@musc.edu (P.A. Flume), claire.wainwright@health.qld.gov.au (C.E. Wainwright), tullis@smh.ca (D.E. Tullis), srodr127@its.jnj.com (S. Rodriguez), minoo_niknian@vrtx.com (M. Niknian), mark_higgins@vrtx.com (M. Higgins), j.c.davies@imperial.ac.uk (J.C. Davies), jeffrey.wagener@ucdenver.edu (J.S. Wagener)

*Corresponding author at: Departments of Medicine and Pediatrics, Medical University of South Carolina, 96 Jonathan Lucas St, Room 812-CSB, MSC 630, Charleston, SC 29425 USA. Tel: +1 843-792-3167
E-mail address: flumepa@musc.edu (P.A. Flume)

Presented at the 36th European Cystic Fibrosis Society (ECFS) Conference, Lisbon, Portugal, 12-15 June 2013.

1
2
3
4 **Abstract (154 Words/Limit 150)**
5

6 *Background:* Pulmonary exacerbations (PE_x) are associated with acute loss of lung function
7 that is often not recovered after treatment. We investigated lung function recovery following PE_x
8 for ivacaftor- and placebo-treated subjects.
9

10
11
12 *Methods:* Short- and long-term pulmonary function recovery data after PE_x were summarized
13 from a placebo-controlled trial in 161 cystic fibrosis patients ≥12 years old with the G551D-
14 CFTR mutation (NCT00909532). Short-term recovery was measured 2 to 8 weeks after
15 treatment, and long-term recovery was determined at the end-of-study, both compared with
16 baseline measured just prior to the PE_x.
17
18
19

20
21
22 *Results:* Fewer patients receiving ivacaftor experienced a PE_x than patients receiving placebo
23 (33.7% vs. 56.4%; $P = 0.004$) and had a lower adjusted incidence rate of PE_x (0.589 vs. 1.382;
24 $P < 0.001$). The proportion of PE_x followed by full short-term recovery of percent predicted
25 forced expiratory volume in 1 s was similar (ivacaftor vs. placebo, 57.1% vs. 53.7), as was the
26 proportion of patients having long-term recovery (46.4% vs. 47.7%).
27
28
29

30
31
32 *Conclusions:* Ivacaftor treatment reduces the frequency of PE_x but does not improve on the rate
33 of complete lung function recovery after PE_x when compared with placebo.
34
35
36

37
38
39
40
41
42 *Keywords:* Cystic fibrosis; Pulmonary exacerbations; Ivacaftor; Cystic fibrosis transmembrane
43 conductance regulator; Pulmonary function
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1. Introduction

Pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF) are associated with a more rapid decline in lung function [1], poorer quality of life [2], increased healthcare costs [3], and early mortality [4, 5]. Although no standardized definition exists [6, 7], in general a PEx is considered to have occurred when a patient presents with increased signs and symptoms of respiratory tract illness, and the clinician decides to begin (or make changes to existing) antibiotic treatment. Avoiding PEx is a key therapeutic goal. When a PEx does occur, loss of lung function frequently occurs [8], and one goal of treatment is to recover this lost function. However, even following treatment and clinical improvement, recovery of lung function is often incomplete [8-13] and accounts for half of the long-term lung function decline in patients with CF [8].

Several factors may contribute to this unrecovered loss of lung function. Although the underlying factors associated with PEx are not always clear, some causes may be more harmful and difficult to treat than others. For example, patients with *Pseudomonas aeruginosa* infection have greater airway inflammation than patients with other bacterial infections and, theoretically, will experience greater airway damage over time [14]. A second factor contributing to PEx-related loss of lung function may be the treatment, either because it is insufficient or delayed; hence, prevention of PEx becomes a key aspect of chronic management. Although antibiotics are almost universally prescribed for PEx, there are no standard approaches for the choice and duration of antibiotic therapy [13, 15]. Finally, host factors, including severity of lung disease, nutritional status, comorbidities, and the use of chronic therapies, may contribute to the impact of PEx. Baseline lung function and the extent of lung function loss associated with PEx may influence the choice of treatment and independently impact the likelihood of recovery [13, 16].

Ivacaftor is a CF transmembrane conductance regulator (CFTR) protein potentiator approved for the treatment of patients with CF who have at least one gating mutation (e.g., *G551D-CFTR*). Ivacaftor targets the underlying disease mechanism in CF, potentiating the

function of the CFTR protein to increase chloride ion secretion in bronchial (and other) epithelial cells, and thereby reducing excess fluid absorption and increasing ciliary beating [17]. In clinical experience, patients receiving ivacaftor have demonstrated improved lung function, improved mucociliary clearance, and lower sputum culture positivity for *P. aeruginosa* [18]. It is plausible that the improvement in mucociliary clearance observed in patients following ivacaftor treatment may enhance the clearance of infective bacteria and inflammatory material following a PEx event, and in so doing also allow for improvement in recovery of lung function after such an event. A placebo-controlled clinical study of ivacaftor in patients with CF ≥ 12 years old (STRIVE) [19] was of sufficient duration to assess the impact of PEx on lung function. We designed this post hoc analysis to assess lung function recovery following a PEx for ivacaftor- and placebo-treated patients.

2. Methods

Data from patients enrolled in the STRIVE clinical study were used in this analysis (NCT00909532). Methods and results for this study were previously reported [19]. STRIVE included 161 patients with CF who had at least one *G551D-CFTR* gene mutation and were ≥ 12 years old, with a baseline percent predicted forced expiratory volume in 1 s (ppFEV₁) of 40 to 90. Patients could not have been treated for PEx in the 4 weeks prior to enrollment. This study lasted 48 weeks, and patients were examined and underwent pulmonary function testing at baseline and at study weeks 2, 8, 16, 24, 32, 40, and 48. Thus, values closest to the PEx were used for analysis. Local ethics committees approved the original protocols, and all patients provided written informed consent or assent, as appropriate.

A PEx was defined a priori as any clinician-determined new or changed antibiotic therapy (intravenous [IV], inhaled, or oral) for four or more protocol-defined signs or symptoms as used by Fuchs et al. [20]. Antibiotic start and stop dates were recorded and were at the clinician's discretion. For analyses of event rates, *P* values were derived from negative binomial

1
2
3
4 regressions that included number of events as the dependent variable, treatment as a fixed
5
6 effect, adjustments for baseline ppFEV₁ severity (<70 vs. ≥70), and age group (<18 years vs.
7
8 ≥18 years), with log (time on study) as an offset. Regressions were only conducted when the
9
10 number of patients with events in each treatment group was five or more and when the model
11
12 converged; otherwise, *P* values were derived from Fisher's exact test on the number of patients
13
14 with events. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary,
15
16 NC, USA).
17

18
19
20 Lung function recovery following PEx was defined as a return to at least 100% of the
21
22 pre-exacerbation ppFEV₁ measurement. Important for this analysis was the lack of pulmonary
23
24 function testing immediately prior to or at the end of a PEx. In order to be included in the lung
25
26 function analysis, patients had to have spirometry results obtained during study visits both
27
28 before and after a PEx; multiple PEx occurring between spirometry measurements were treated
29
30 as one event for the purposes of lung function recovery analyses. Short-term recovery was
31
32 calculated for each PEx by comparing the most recent pre-exacerbation ppFEV₁ with that
33
34 measured 2 to 8 weeks after stopping the new or changed antibiotic. Long-term recovery was
35
36 determined by the change in ppFEV₁ from the pre-exacerbation value to the end-of-study value
37
38 (duration varied depending on when during the study the PEx occurred). Long-term recovery
39
40 was calculated only once (using the first PEx) for patients with more than one PEx. Lung
41
42 function recovery data were also summarized according to the number of observed PEx events
43
44 and from patients treated with IV antibiotics, whether or not they met the a priori criteria for a
45
46 PEx.
47
48
49
50
51
52

53 **3. Results**

54
55 Baseline demographics demonstrated that the 83 ivacaftor- and 78 placebo-treated
56
57 patients were well matched for age, sex, nutritional status, ppFEV₁ (mean ± SD, 63.5 ± 16.1 vs.
58
59 63.7 ± 16.8), and sweat chloride [19].
60
61
62
63
64
65

Overall, fewer patients in the ivacaftor group had PEx events reported during the study period ($n = 28$ [33.7%]) than in the placebo group ($n = 44$ [56.4%]; $P = 0.004$), and more patients in the placebo group experienced three or more PEx ($n = 14$ [17.9%]) than the ivacaftor group ($n = 4$ [4.8%]; $P = 0.01$; Fig. 1). The rate of pulmonary exacerbations (1.382 and 0.589 for placebo and ivacaftor, respectively) was 57.4% lower in the ivacaftor group than in the placebo group (rate ratio [95% confidence interval (CI)], 0.426 [0.268–0.676]; $P < 0.001$; Table 1) and the rate of sinopulmonary signs and symptoms (2.577 and 1.477 for placebo and ivacaftor, respectively) was 42.7% lower in the ivacaftor group than in the placebo group (rate ratio [95% CI], 0.573 [0.423–0.776]; $P < 0.001$). The frequency of specific signs and symptoms that were associated with PEx events in patients receiving ivacaftor and placebo are shown in Table 2. Overall, increased cough was the most frequently reported symptom, with the other most common symptoms being a change in sputum, malaise/fatigue/lethargy, and increased dyspnea.

The mean number of days with PEx per patient (normalized for time on study) in the ivacaftor group was significantly less than in the placebo group (mean normalized days with PEx per patient, 13.5 vs. 36.7; $P < 0.001$; Table 1). Of the 146 PEx events recorded during the study (99 in the placebo group and 47 in the ivacaftor group), 75 (51.4%) were treated with IV antibiotics, and 52 (35.6%) were treated by inpatient hospitalization. As shown in Table 1, the proportion of patients with PEx treated with IV antibiotics and the proportion undergoing hospitalization were greater in the placebo group than the ivacaftor group ($P = 0.02$ and $P = 0.01$, respectively); no significant difference in events treated by hospitalization was detected ($P = 0.19$). Additionally, considering all patients in both treatment groups, the mean duration of IV antibiotic therapy for PEx (normalized for time on study) was shorter in the ivacaftor group than in the placebo group ($P = 0.02$; Table 1).

As noted above, more patients in the placebo group ($n=44$) experienced ≥ 1 PEx during the study than in the ivacaftor group ($n=28$). For those patients experiencing ≥ 1 PEx,

1
2
3
4 demographics and baseline characteristics were well-balanced for age, sex, nutritional status,
5
6 ppFEV₁, and sweat chloride; mean ppFEV₁ preceding the first PEx was higher in the ivacaftor
7
8 group (Table S1).
9

10
11 The proportion of patients with complete (i.e., ≥100%) long-term ppFEV₁ recovery was
12
13 similar in the ivacaftor and placebo groups (46.4% vs. 47.7%; Fig. 2A). For the short-term
14
15 recovery analysis, multiple PEx occurring between two spirometry assessments were collapsed
16
17 into single events, such that there were 54 qualifying events in the placebo group and 28 in the
18
19 ivacaftor group. The proportion of these events followed by complete short-term ppFEV₁
20
21 recovery was similar in the ivacaftor and placebo groups (57.1% vs. 53.7%; Fig. 2B).
22
23

24
25 In the analyses described above we included all PEx, including those treated with IV and
26
27 oral antibiotics. To investigate the impact of antibiotic treatment on recovery from PEx we
28
29 performed additional analyses comparing the groups based on all patients treated with IV
30
31 antibiotics specifically for a PEx, all patients treated with any antibiotic (i.e., they did not meet
32
33 the full criteria of a PEx), and all patients with one or more sign or symptom treated with IV
34
35 antibiotics. We found no differences in long-term recovery of lung function between the groups
36
37 in any of these comparisons (Table S2). As patients in the placebo group were more likely to
38
39 experience more than one PEx than those in the ivacaftor group, we also looked for differences
40
41 in rates of lung function recovery between the groups using only those patients with just one
42
43 PEx, but found none (Table S2). By the end of 48 weeks, patients who received ivacaftor and
44
45 had multiple PEx experienced benefits in ppFEV₁ (Figure 3) and other spirometric measures of
46
47 lung function (Table S3), as did patients who received ivacaftor and had no PEx, whereas
48
49 patients who received placebo had near-baseline or a decline in lung function, regardless of the
50
51 number of PEx.
52
53
54
55
56
57
58
59
60
61
62
63
64
65

4. Discussion

In this post hoc analysis of a placebo-controlled study, patients ≥ 12 years old with CF and a *G551D-CFTR* gene mutation who were treated with ivacaftor had a reduced frequency of PEx, were less likely to experience a PEx, and less likely to experience three or more PEx during the study period than patients treated with placebo. Further, a smaller proportion of patients receiving ivacaftor experienced PEx treated with IV antibiotics and a smaller proportion underwent inpatient hospitalization than patients receiving placebo. Overall, patients in the ivacaftor group demonstrated substantial lung function improvement regardless of PEx incidence, but there was no apparent difference (vs. placebo) in the likelihood to recover function fully after a PEx.

For this analysis, we defined lung function recovery as a return to at least 100% of the patient's pre-exacerbation $ppFEV_1$, whereas other studies have used different standards for recovery. Sanders et al. [12] defined a responder as achieving 95% of baseline FEV_1 within 3 months of ending a hospitalization for a PEx and found that 23% of children did not recover. When they looked for 100% recovery to baseline, 42.3% of patients did not achieve this goal. Our finding that 46.3% and 42.9% of patients in the placebo and ivacaftor groups, respectively, did not recover to 100% of their pre-exacerbation FEV_1 by 2 to 8 weeks following a PEx is strikingly similar, although our analysis did not require hospitalization and included both IV and oral antibiotic-treated patients. This lack of recovery among both IV and oral antibiotic-treated patients is consistent with epidemiologic findings showing that both short-term and long-term loss of lung function occurs regardless of the choice of antibiotics [13].

In a subsequent study by Sanders et al. using US Cystic Fibrosis Foundation Patient Registry data (for patients aged ≥ 6 years) and defining recovery as 90% of baseline lung function [21], 25% of patients failed to recover within 3 months of a hospitalization for a PEx. Furthermore, 58% of these patients who failed to recover still had not recovered to 90% of

1
2
3
4 baseline function by 1 year following the PEx. Again, the results of our post hoc analysis are
5
6 similar: there were patients in both the ivacaftor (53.6%) and placebo (52.3%) groups who failed
7
8 to achieve their pre-exacerbation lung function by the end of 48 weeks. However, in the present
9
10 study our goal was 100% of pre-exacerbation lung function, and we included all patients in our
11
12 48-week analysis, whereas in Sanders et al. [21], patients who recovered to 90% function by 3
13
14 months after PEx were excluded from the 6- and 12-month analyses. It should be noted that our
15
16 definition of long-term recovery as a return to $\geq 100\%$ of the pre-exacerbation FEV₁ value does
17
18 not account for potential lung function decline that can occur independently of PEx in the
19
20 context of CF as a progressive disease.
21
22

23
24 The strength of our analysis is that these data were captured during a placebo-controlled
25
26 trial with scheduled visits, whereas previous studies have typically used registry data obtained
27
28 during usual clinical care. However, this study was not specifically designed to address changes
29
30 in the severity or nature of PEx or time to lung function recovery after PEx. Additionally, patients
31
32 described here were initially assessed during a period of stability, establishing a true baseline
33
34 for lung function rather than using the highest recorded value in the registry as the patient's
35
36 baseline. Since patients often experience an acute increase in lung function with ivacaftor
37
38 treatment, we based our recovery calculation on the FEV₁ immediately prior to a PEx, with the
39
40 assumption that this newer, often higher value was their new baseline. Finally, so that these
41
42 results (using a protocol-defined definition of a PEx) can be compared with results from
43
44 epidemiologic studies, we looked at multiple subsets of patients; we saw similar results when
45
46 we analyzed data restricted to patients who were treated with IV antibiotics.
47
48
49
50

51 A recent study of long-term ivacaftor use has shown a reduction in the rate of decline of
52
53 lung function [22], suggesting that CFTR modulation modifies disease progression. Our results
54
55 demonstrate that the adverse outcomes attributed to PEx (i.e., loss of lung function) occur even
56
57 when addressing the underlying cause of CF and improving CFTR function in the host (though
58
59 not to the level of function of wild-type CFTR [17]). Since no therapy has proven to be effective
60
61
62
63
64
65

1
2
3
4 in reversing lung function loss following a PEx, prevention should be a high priority. Indeed,
5
6 ivacaftor has been shown to reduce the incidence of PEx both in clinical trials [19] and in the
7
8 setting of real-world clinical practice [23]. It may be noted that multiple studies of therapies
9
10 directed at airway disease in CF such as hypertonic saline and the antibiotics azithromycin and
11
12 inhaled tobramycin have shown a reduction in PEx frequency; however, those studies did not
13
14 assess the therapeutic impact on recovery [24-26].
15
16

17 Collectively, these data suggest that altering host tissue physiology by modifying CFTR
18
19 function with ivacaftor does not prevent the adverse impact of PEx on lung function.
20
21

22 Nonetheless, in patients treated with ivacaftor who had one or more PEx, there was a large
23
24 improvement in ppFEV₁ at the end of the study compared with their original baseline, whereas
25
26 in patients receiving placebo there was no improvement. This suggests that the change in
27
28 CFTR function produced by ivacaftor may affect patients in a way that results in long-term
29
30 disease modification but does not affect the way lung tissue responds to acute PEx and their
31
32 treatment. One can theorize in terms of mechanism that the long-term benefits of improved
33
34 mucociliary clearance may be overwhelmed by airway injury during a PEx.
35
36

37 For this analysis we used a pragmatic definition of a PEx. The combination of clinician
38
39 decision to treat and the detection of multiple signs or symptoms has long been used in other
40
41 reports of PEx [20]. Although this definition is not a standardized one and there has long been
42
43 an interest in deriving such a definition as it could standardize practice, the definition used in
44
45 this analysis is consistent with clinical practice. An important limitation of the present analysis is
46
47 that the STRIVE clinical study was not designed to assess lung function recovery outcomes
48
49 following PEx. Assessment of short- and long-term recovery from PEx represents a post hoc
50
51 analysis in which the subgroups (those with PEx) were outcomes related to treatment allocation,
52
53 such that the patients who received ivacaftor and had PEx may be different to those who
54
55 received placebo and had PEx. Therefore the findings should be considered exploratory and
56
57 interpreted with caution. It should also be noted that specific information was not collected
58
59
60
61
62
63
64
65

1
2
3
4 during the STRIVE study regarding the etiology underlying PEx events, the specific antibiotics
5 used, or the utilization of other PEx treatments. Additionally, microbiology data were only
6 available at baseline, and no FEV₁ measurements during the PEx were recorded.
7
8
9

10
11 In conclusion, patients aged ≥12 years old with CF and a *G551D-CFTR* gene mutation
12 receiving ivacaftor were less likely to experience any PEx and experienced fewer PEx events
13 versus those receiving placebo. However, the proportion of patients with complete lung function
14 recovery in the short term and long term following a PEx was similar in the ivacaftor and
15 placebo groups. This finding suggests that addressing the underlying cause of CF disease by
16 altering CFTR protein function does reduce the incidence and duration of PEx and improve
17 long-term lung health, even when PEx do occur, but appears to have no measurable effect on
18 the likelihood of 100% recovery of pre-exacerbation lung function following a PEx.
19
20
21
22
23
24
25
26
27
28
29
30

31 **Funding**

32
33 This study was sponsored by Vertex Pharmaceutical Incorporated.
34

35 P.A. Flume's research time was supported by the South Carolina Clinical & Translational
36 Research (SCTR) Institute, with an academic home at the Medical University of South Carolina,
37 through NIH grant number UL1 TR001450. D.E. Tullis' research time was supported by the
38 Cystic Fibrosis Canada Chair in Adult CF Research. J.C. Davies' research time was supported
39 by the National Institute of Health Research, Respiratory Biomedical Research Unit at the Royal
40 Brompton and Harefield, NHS Foundation Trust and Imperial College, London.
41
42
43
44
45
46
47
48
49
50

51 **Conflict of interest**

52
53 M. Niknian and M. Higgins are employees of Vertex Pharmaceuticals Incorporated and may
54 own stock or stock options in that company. J.S. Wagener and S. Rodriguez were previously
55 employed by Vertex Pharmaceuticals Incorporated and may own stock or stock options in that
56 company. P.A. Flume, C.E. Wainwright, D.E. Tullis, J.C. Davies, and J.S. Wagener have
57
58
59
60
61
62
63
64
65

1
2
3
4 consulted for, and their institutions have received research funding from, Vertex
5
6 Pharmaceuticals Incorporated.
7
8
9

10 **Author contributions**

11
12 P.A. Flume, S. Rodriguez, and J.S. Wagener contributed to the study design. All authors
13 participated in data analysis/interpretation and critical review and revision of the manuscript.
14
15 P.A. Flume and J.S. Wagener participated in project management. S. Rodriguez, M. Niknian,
16
17 and J.S. Wagener participated in data management and statistical analysis. All authors
18
19 approved the final draft for submission.
20
21
22
23
24
25

26 **Acknowledgments**

27
28 We thank the patients and their families who participated in the clinical study, as well as
29
30 Elizabeth Dorn, PhD, and Dhrupad Patel, PharmD, from Vertex Pharmaceuticals Incorporated,
31
32 who assisted with manuscript preparation, and Bonnie Bielefeld, MS, an employee of
33
34 BioBridges, for statistical programming and data review support. Medical writing and editorial
35
36 support were provided by Jeremy Kennard, PhD, Dena McWain, and Shannon Davis of Ashfield
37
38 Healthcare Communications, which received funding from Vertex Pharmaceuticals
39
40 Incorporated.
41
42
43
44
45

46 **Supplementary data to this article can be found online at XXXX.**

47
48 Data includes:
49

50
51 Table S1. Demographics, baseline characteristics, and ppFEV₁ preceding first PEx for patients
52
53 who had ≥1 PEx during study
54

55
56 Table S2. Proportion of patients with full (≥100%) recovery of lung function following treatment
57
58 of protocol-defined PEx
59

60
61 Table S3. Change from baseline in spirometry measures at week 48
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References

- [1] Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* 2007;151(2):134-9, 9 e1.
- [2] Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002;121(1):64-72.
- [3] Lieu TA, Ray GT, Farmer G, Shay GF. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics* 1999;103(6):e72.
- [4] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;153(4):345-52.
- [5] Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *Am J Respir Crit Care Med* 2002;166(12 Pt 1):1550-5.
- [6] Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. *J Pediatr* 2006;148(2):259-64.
- [7] Bilton D, Canny G, Conway S, Dumcius S, Hjelte L, Proesmans M, et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. *J Cyst Fibros* 2011;10(Suppl 2):S79-81.
- [8] Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* 2012;40(1):61-6.
- [9] Collaco JM, Green DM, Cutting GR, Naughton KM, Mogayzel PJ, Jr. Location and duration of treatment of cystic fibrosis respiratory exacerbations do not affect outcomes. *Am J Respir Crit Care Med* 2010;182(9):1137-43.

- 1
2
3
4 [10] Heltshe SL, Goss CH, Thompson V, Sagel SD, Sanders DB, Marshall BC, et al. Short-
5 term and long-term response to pulmonary exacerbation treatment in cystic fibrosis. Thorax
6 2015;71(3):223-9.
7
8
9
10 [11] Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations
11 are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis.
12 Pediatr Pulmonol 2011;46(4):393-400.
13
14
15 [12] Sanders DB, Hoffman LR, Emerson J, Gibson RL, Rosenfeld M, Redding GJ, et al.
16 Return of FEV₁ after pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol
17 2010;45(2):127-34.
18
19
20 [13] Wagener JS, Rasouliyan L, VanDevanter DR, Pasta DJ, Regelman WE, Morgan WJ, et
21 al. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic
22 fibrosis. Pediatr Pulmonol 2013;48(7):666-73.
23
24
25 [14] Sagel SD, Gibson RL, Emerson J, McNamara S, Burns JL, Wagener JS, et al. Impact of
26 Pseudomonas and Staphylococcus infection on inflammation and clinical status in young
27 children with cystic fibrosis. J Pediatr 2009;154(2):183-8.
28
29
30 [15] Flume PA, Mogayzel PJ, Robinson KA, Goss CH, Rosenblatt R, Kuhn R, et al. Cystic
31 Fibrosis Pulmonary Guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care
32 Med 2009;180(9):802-8.
33
34
35 [16] Morgan WJ, Wagener JS, Yegin A, Pasta DJ, Millar SJ, Konstan MW, et al. Probability
36 of treatment following acute decline in lung function in children with cystic fibrosis is related to
37 baseline pulmonary function. J Pediatr 2013;163(4):1152-7 e2.
38
39
40 [17] Van Goor F, Hadida S, Grootenhuys PD, Burton B, Cao D, Neuberger T, et al. Rescue of
41 CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S
42 A 2009;106(44):18825-30.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

- [18] Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. *Am J Respir Crit Care Med* 2014;190(2):175-84.
- [19] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365(18):1663-72.
- [20] Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331(10):637-42.
- [21] Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010;182(5):627-32.
- [22] Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med* 2015;192(7):836-42.
- [23] Hassan M, Bonafede MM, Limone BL, Hodgkins P, Suthoff ED, Sawicki G. Reduction in pulmonary exacerbations (PE_x) after initiation of ivacaftor: a retrospective cohort study among patients with cystic fibrosis (CF) treated in real-world settings. *J Cyst Fibros* 2016;15(Suppl 1):S58.
- [24] Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354(3):229-40.
- [25] Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;340(1):23-30.

- 1
2
3
4 [26] Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al.
5
6 Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*:
7
8 a randomized controlled trial. JAMA 2003;290(13):1749-56.
9
10
11 [27] VanDevanter DR, Flume PA, Morris N, Konstan MW. Probability of IV antibiotic
12
13 retreatment within thirty days is associated with duration and location of IV antibiotic treatment
14
15 for pulmonary exacerbation in cystic fibrosis. J Cyst Fibros 2016;15(6):783-90
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

TABLES

Table 1

Protocol-defined PEx over a 48-week period.

PEx event	Placebo (n = 78)	Ivacaftor (n = 83)	<i>P</i> value ^a
Patients with events, n (%)	44 (56.4)	28 (33.7)	0.004
Number of events, n (event rate) ^b	99 (1.382)	47 (0.589)	<0.001 ^c
Normalized days per patient with events, mean ± SD ^d	36.67 ± 49.537	13.54 ± 27.269	<0.001 ^e
Number of patients treated with IV antibiotics for PEx, n (%) ^f	27 (34.6)	15 (18.1)	0.02
Normalized days per patient of IV antibiotic therapy for PEx, mean ± SD ^{d,f}	11.03 ± 20.355	6.68 ± 19.429	0.02 ^e
Number of events treated with IV antibiotic therapy, n (event rate) ^{b,f}	47 (0.711)	28 (0.397)	0.08 ^c
Number of patients undergoing hospitalization for PEx, n (%)	23 (29.5)	11 (13.3)	0.01
Number of events treated by hospitalization, n (event rate) ^b	31 (0.489)	21 (0.311)	0.19 ^c

^aUnless otherwise stated (^c, ^e), *P* values are from Fisher's exact test.

^bEstimates of event rates were obtained from negative binomial regression with the number of events as the dependent variable, treatment as a fixed effect, and adjustment for baseline ppFEV₁ severity (<70 vs ≥70), and age group (<18 vs ≥18 years), with log (time on study) as an offset.

^c*P* values are from the treatment effect in negative binomial regression.

^dNormalized days are defined as days with events adjusted for time spent in the study by multiplying the observed proportion of days with events by the total study days expected (i.e., 336 days for 48 weeks).

^e*P* values are from a stratified (by baseline ppFEV₁ severity and age group) Wilcoxon rank-sum test.

^fThe use of IV antibiotics includes events treated at home or in hospital.

IV, intravenous; PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s; SD, standard deviation.

Table 2

Signs and symptoms reported in patients who experienced a protocol-defined PEx

	Placebo (n = 44) [99 events]	Ivacaftor (n = 28) [47 events]
Clinical sign or symptom	n (%)	n (%)
Increased cough	95 (96.0)	46 (97.9)
Change in sputum	83 (83.8)	40 (85.1)
Malaise, fatigue, or lethargy	62 (62.6)	38 (80.9)
Increased dyspnea	55 (55.6)	27 (57.4)
Chest examination (change)	34 (34.3)	19 (40.4)
10% drop in FEV ₁	31 (31.3)	11 (23.4)
Sinus discharge (change)	29 (29.3)	12 (25.5)
Temperature >38°C	20 (20.2)	12 (25.5)
Sinus pain or tenderness	19 (19.2)	11 (23.4)
Anorexia or weight loss	21 (21.2)	8 (17.0)
Hemoptysis (new or increased)	13 (13.1)	10 (21.3)
Radiographic changes of new pulmonary infection	10 (10.1)	1 (2.1)

FEV₁, forced expiratory volume in 1 s; PEx, pulmonary exacerbation.

FIGURES

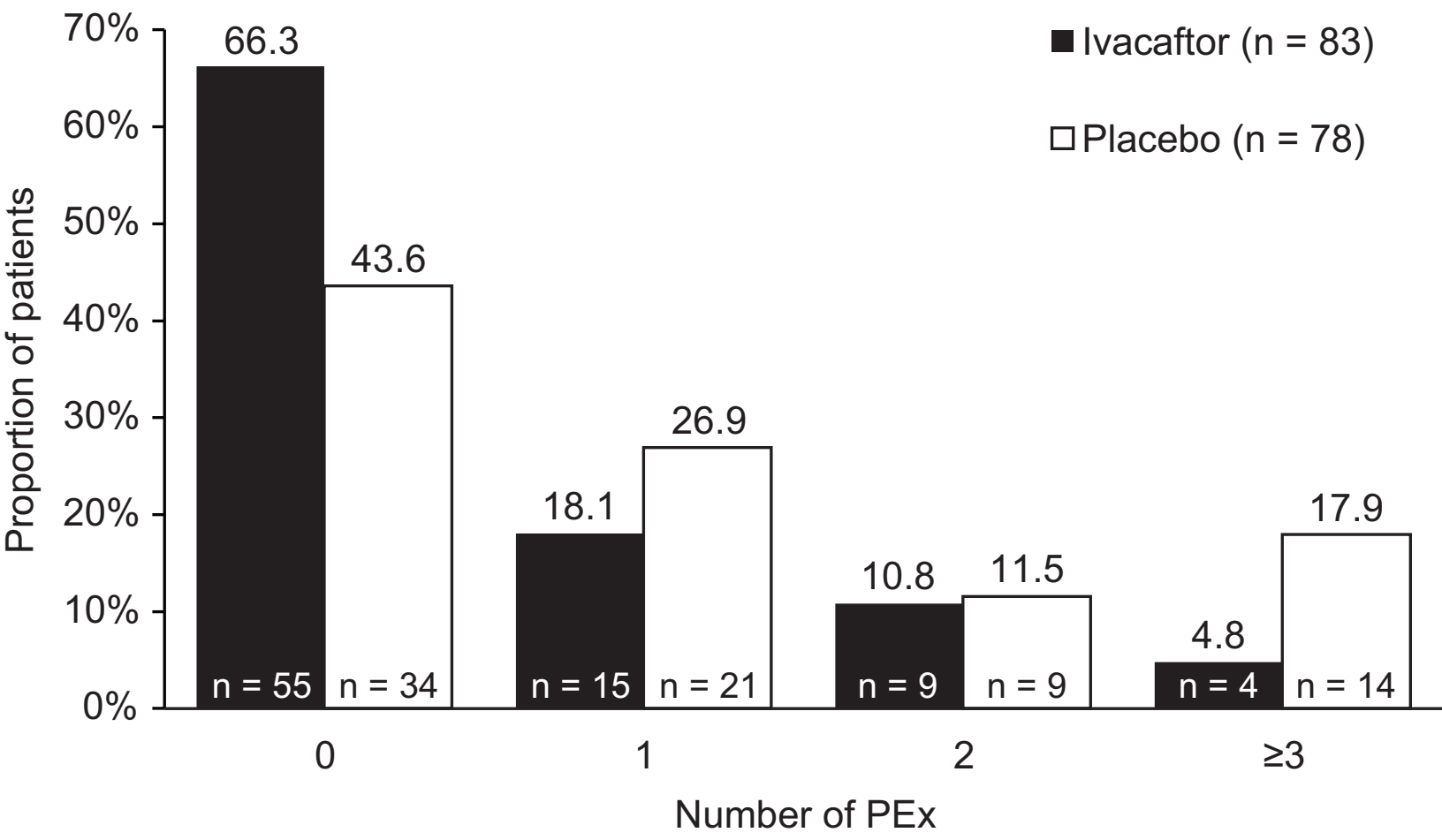
Fig. 1. Percentage of patients in the STRIVE study by number of protocol-defined PEx. PEx, pulmonary exacerbations.

Fig. 2. Proportion of patients experiencing protocol-defined PEx with full long-term functional recovery (A) and proportion of protocol-defined PEx events followed by full short-term functional recovery (B). Long-term recovery is defined as the return to $\geq 100\%$ of pre-exacerbation ppFEV₁ at end of study participation (week 48 or last on-treatment visit; shown as proportion of total number of patients experiencing PEx, panel A). Short-term recovery is defined as the return to $\geq 100\%$ of pre-PEx ppFEV₁ within 2 to 8 weeks after event (shown as proportion of total PEx events, panel B).

PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s.

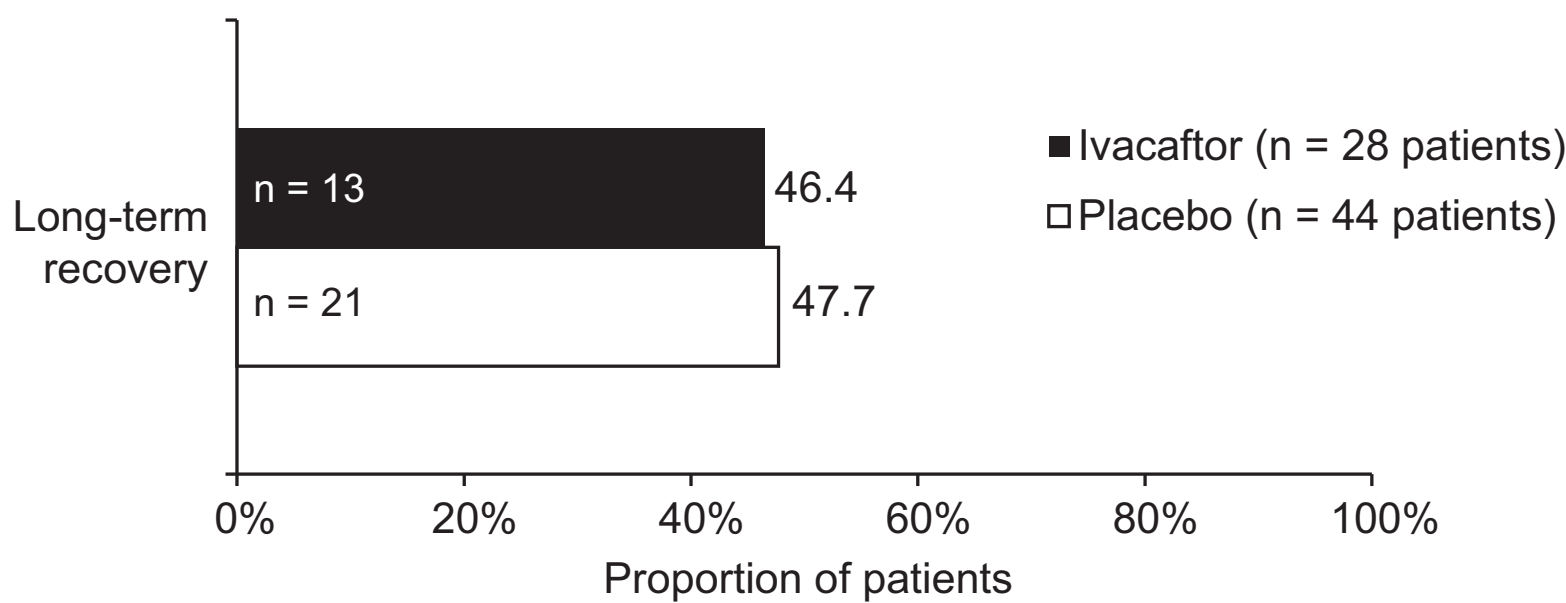
Fig. 3. Improvement from study baseline in ppFEV₁ at week 48 by number of protocol-defined PEx. Data are shown for patients with non-missing FEV₁ measurements at week 48. FEV₁, forced expiratory volume in 1 s; PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s.

Figure(s)

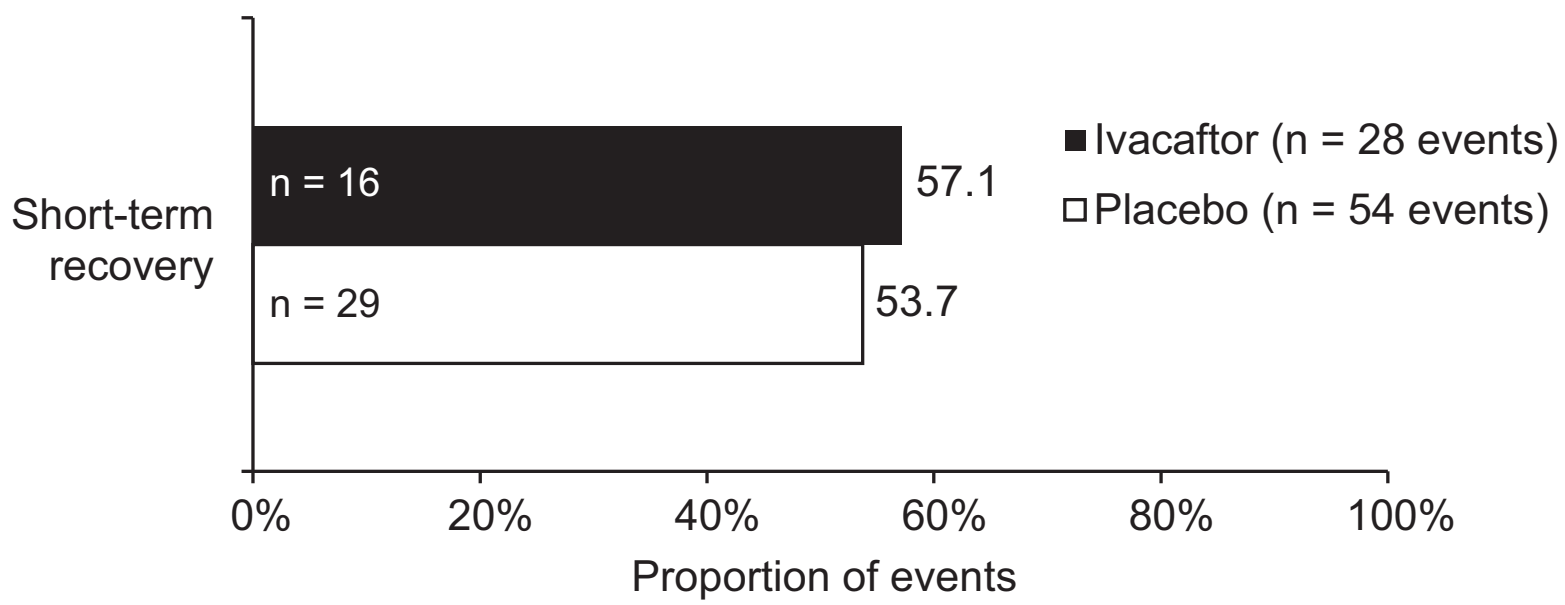


Figure(s)

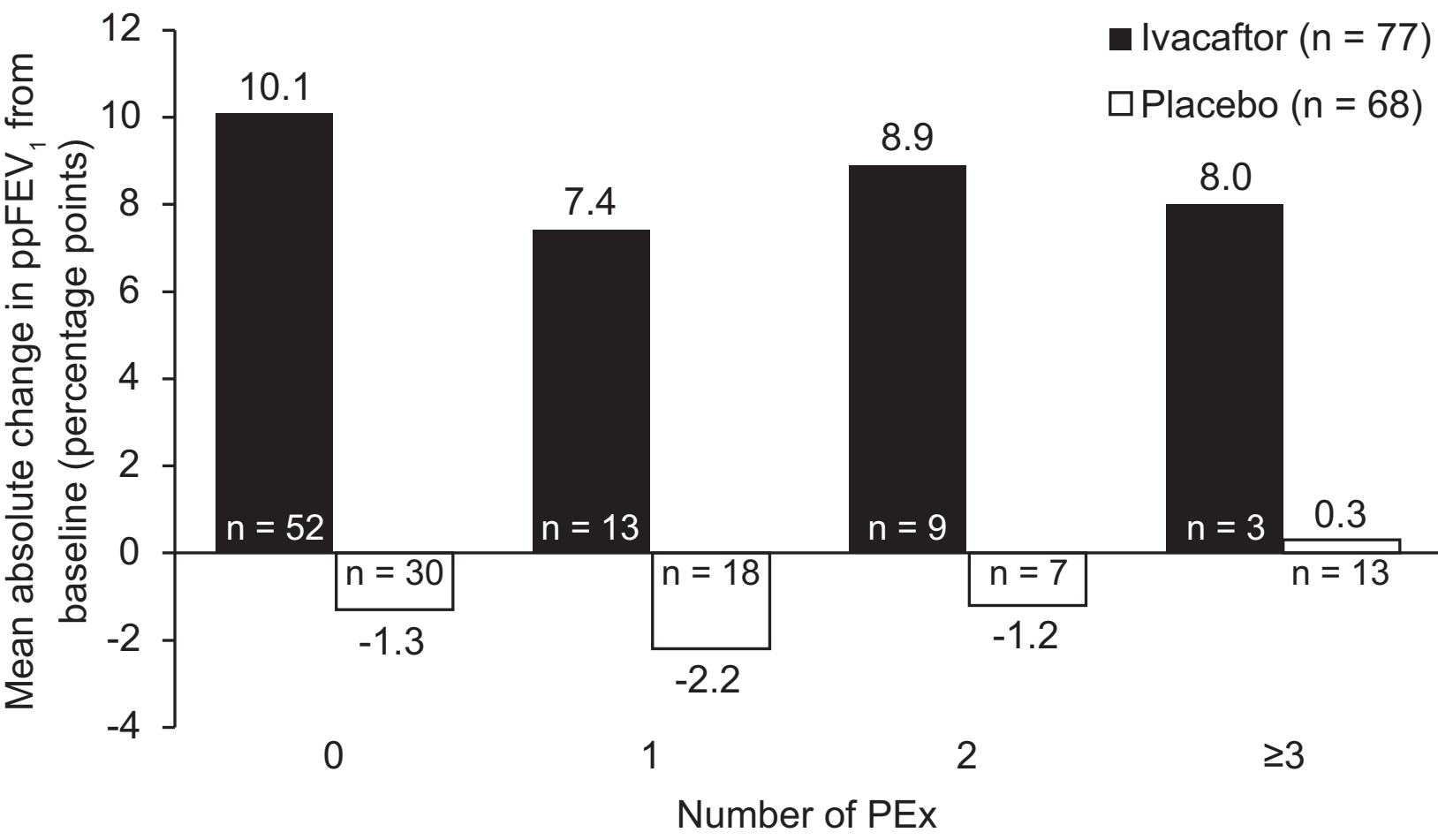
A



B



Figure(s)



Supplement

[Click here to download Supplementary Material: Flume_STRIVE PEx and FEV1_JCystFibr_Supplmtl_5April2017_FINAL.docx](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: coi_disclosure - TULLIS, E.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: coi_disclosure davies.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: coi_disclosure_Flume.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: coi_disclosure_Higgins.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: coi_disclosure_Niknian.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: coi_disclosure_Rodriguez.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: COI_Wagener 2017.pdf](#)

***Conflict of Interest statement**

[Click here to download Conflict of Interest statement: ICMJE COI Wainwright Feb 2017.pdf](#)