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Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1

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Abstract

Background: Improved lung function and fewer pulmonary exacerbations (PEx) were observed with lumacaftor/ivacaftor (LUM/IVA) in patients with cystic fibrosis homozygous for *F508del*. It is unknown whether PEx reduction extends to patients without early lung function improvement.

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Methods: Post hoc analyses of pooled phase 3 data (NCT01807923, NCT01807949) categorized LUM/IVA-treated patients by percent predicted forced expiratory volume in 1 second ($ppFEV_1$) change from baseline to day 15 into threshold categories (absolute change ≤0 vs >0; relative change <5% vs ≥5%) and compared PEx rates vs placebo.

Results: LUM (400 mg q12h)/IVA (250 mg q12h)–treated patients (n=369) experienced significantly fewer PEx vs placebo, regardless of threshold category. With LUM/IVA, PEx rate per patient per year was 0.60 for those with absolute change in $ppFEV_1$ >0 and 0.85 for those with absolute change ≤0 (respective rate ratios vs placebo [95% CI]: 0.53 [0.40–0.69; P<0.0001], 0.74 [0.55–0.99; P=0.0441]).

Conclusions: LUM/IVA significantly reduced PEx, even in patients without early lung function improvement.

Keywords

cystic fibrosis; pulmonary exacerbations; percent predicted forced expiratory volume in 1 second; lumacaftor; ivacaftor

1. INTRODUCTION

In patients with cystic fibrosis (CF), pulmonary exacerbations (PEx) are characterized by acute worsening of pulmonary symptoms, decreased pulmonary function, fatigue, and weight loss [1,2]. Pulmonary exacerbations are associated with a progressive loss of lung function [3–7], a negative impact on quality of life [8, 9], and an increased risk of future PEx [10,11]. Importantly, PEx are a significant, independent predictor of mortality in patients with CF [12–14].

Management of PEx often involves intravenous (IV) antibiotic therapy and hospitalization [15]. According to the US CF Patient Registry 2015 Annual Data Report, the median (range) total duration of IV antibiotic therapy for PEx was 14.0 (5.0–27.0) days for those aged 18 years and older, with a median (range) of 8.3 (4.0–14.3) days spent in the hospital [15]. Reducing PEx is an important therapeutic goal in patients with CF and may help to decrease morbidity and mortality [2,7,10,11]. However, even with extensive IV antibiotic therapy and lengthy hospitalizations, PEx in patients with CF are associated with a progressive decrease in lung function, which is often irreversible [4,5,7].

Recent therapeutic approaches have targeted the underlying mechanism of CF [16,17]. Cystic fibrosis is caused by mutations in the CF transmembrane conductance regulator (CFTR) ion channel that disrupt the balance of ions, resulting in altered viscosity of luminal secretions in a variety of organs [18]. The most common CF-causing mutation in CFTR, *F508del*, results in both a primary folding defect and a secondary chloride-conductance defect [17]. In two 24-week, phase 3 studies (TRAFFIC and TRANSPORT) with identical study designs, treatment with a combination of lumacaftor (LUM), a folding corrector, and ivacaftor (IVA), a potentiator, significantly improved percent predicted forced expiratory volume in 1 second ($ppFEV_1$; primary endpoint) from 2.6 to 4.0 percentage points compared with placebo in patients aged ≥12 years with CF who were homozygous for the *F508del* mutation (P<0.001) [17].

The rate of PEx after 24 weeks of LUM/IVA therapy in all patients with CF who were homozygous for the *F508del* mutation was 30% to 39% lower compared with placebo ($P \leq 0.001$) [17]. However, it is unknown if the beneficial effects on PEx outcomes extend to the subset of patients with little or no improvement in $ppFEV_1$ during the first 2 weeks of treatment or is different by subgroups related to age, sex, and other baseline characteristics. The goal of this analysis was to determine whether there was an improvement in PEx (rate, severity, and number of days) in LUM/IVA-treated patients with little or no early improvement in $ppFEV_1$ when compared with placebo-treated patients, using a post hoc analysis of pooled data from the TRAFFIC and TRANSPORT studies, or whether the impact of LUM/IVA on PEx differed by baseline subgroups.

2. METHODS AND MATERIALS

The full methodology and results of TRAFFIC and TRANSPORT have been previously reported [17]. Briefly, TRAFFIC and TRANSPORT were phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group studies with identical study designs conducted between April 2013 and April 2014 (Clinicaltrials.gov identifiers: NCT01807923 and NCT01807949). The studies were conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines and with local applicable laws and regulations. Each patient and/or their caregiver provided written informed consent before study participation. Eligible patients had a confirmed diagnosis of CF, were homozygous for the *F508del* mutation, were ≥12 years of age, and had an FEV_1 of predicted normal values of 40% to 90% (inclusive) at screening. Patients were randomized 1:1:1 to receive treatment with LUM 600 mg once daily with IVA 250 mg once every 12 hours (LUM 600 mg qd/IVA 250 mg q12h), LUM 400 mg q12h/IVA 250 mg q12h, or matching placebo for 24 weeks.

The primary endpoint in TRAFFIC and TRANSPORT was the absolute change from baseline in $ppFEV_1$ through 24 weeks of LUM/IVA treatment, which was calculated by averaging the mean absolute change at weeks 16 and 24 [17]. Key secondary endpoints in TRAFFIC and TRANSPORT included the percentage of patients with a relative increase from baseline in $ppFEV_1$ ≥5% and the number of PEx through week 24 (expressed as a rate over 48 weeks; inclusive of events that happened on treatment and after treatment discontinuation). The total number of days receiving IV antibiotics and the total number of days hospitalized for PEx events were recorded through week 24. Although there is no universally accepted standard for the diagnosis or treatment of PEx [19–21], a standardized definition was used in the clinical studies. A PEx event was defined as new or changed antibiotic therapy for any 4 or more of the following sinopulmonary signs or symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature >38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; or radiographic changes indicative of a pulmonary infection [16,22].

2.1 Outcomes analyses

Prespecified pooled subgroup analyses, defined according to TRAFFIC and TRANSPORT [17] baseline characteristics including age, $ppFEV_1$, select CF-related medications, and select infections, were performed for the key secondary endpoint of number of PEx through week 24 for LUM/IVA-treated patients vs those receiving placebo.

Post hoc analyses assessed the rates of PEx stratified by early changes in $ppFEV_1$ for patients treated with LUM/IVA vs placebo; patients in the active treatment groups were categorized by their change in $ppFEV_1$ from baseline to day 15 (ie, into threshold categories). Threshold categories were specified for change in $ppFEV_1$ from baseline to day 15: absolute change in $ppFEV_1$ ≤0 vs >0 percentage points and relative change in $ppFEV_1$ <5% vs ≥5%. Pulmonary exacerbation event rates and total number of days with a PEx event per patient per 48 weeks were calculated for each threshold category and for placebo; 48 weeks was considered equivalent to 1 year for the analysis. Analyses were conducted for all PEx events as well as those requiring treatment with IV antibiotics and hospitalization. Rate ratios for event rates were calculated for each threshold category vs placebo, and number of days with PEx was compared between the threshold groups treated with LUM/IVA and those treated with placebo.

Because of the interdependence of $ppFEV_1$ and PEx in CF and methodologic limitations whereby the outcome of interest (in this case, PEx) may occur before the stratification variable (in this case, change from baseline in $ppFEV_1$), the earliest postbaseline $ppFEV_1$ measure (day 15) was used in these analyses of PEx outcomes to minimize confounding. Exploratory assessments categorizing patients based on the change from baseline in $ppFEV_1$ at different time points (week 4 and the average of weeks 16 and 24) were also performed.

2.2 Statistical analyses

All patients who were randomized and received at least 1 dose of study drug were included in the analysis. Prespecified pooled subgroup analyses of PEx rates by baseline characteristics were performed using a negative binomial regression model that included study, treatment, sex, age, and $ppFEV_1$ severity at screening (<70 vs ≥70; omitting the corresponding variables of sex, age, and $ppFEV_1$ severity from the model when performing those particular subgroup analyses), with the log of time spent in the study as an offset.

For the analyses by threshold group, event rates and rate ratios were calculated using negative binomial regression models that included study, treatment category (placebo, LUM 400 mg q12h/IVA 250 mg q12h, or LUM 600 mg qd/IVA 250 mg q12h + threshold category [absolute change in $ppFEV_1$ ≤0 vs >0 or relative change in $ppFEV_1$ <5% vs ≥5%]), sex, age (<18 vs ≥18 years), and $ppFEV_1$ severity at screening (<70 vs ≥70), with the log of time spent in the study treated as an offset. A negative binomial regression model was also used to predict the number of PEx events based on absolute change from baseline in $ppFEV_1$ at day 15 as a continuous variable; the model included study, sex, age (<18 vs ≥18 years), $ppFEV_1$ severity at screening (<70 vs ≥70), and absolute change from baseline in $ppFEV_1$ at day 15, with the log of time spent in the study treated as an offset.

A comparison of the annualized proportion of days with PEx events for each threshold category vs placebo was assessed using a Wilcoxon rank sum test stratified by study, sex, age, and $ppFEV_1$ at screening. The total number of days was normalized for time spent in the study by multiplying the observed proportion of days with event by the total number of expected study days (eg, 168 days for 24 weeks). Data reported here are for the commercially available dose of LUM/IVA (LUM 400 mg q12h/IVA 250 mg q12h). Data for the LUM 600 mg qd/IVA 250 mg q12h dose are reported in the online data supplement.

3. RESULTS

In TRAFFIC and TRANSPORT [17], 1446 patients were screened, 1122 of whom were randomized. In total, 1108 patients received at least 1 dose of study drug and were included in this analysis. When measured at day 15, 146 of the 369 patients who received LUM 400 mg q12h/IVA 250 mg q12h had an absolute change in $ppFEV_1$ ≤0 and 223 had an absolute change >0; 228 patients had a relative change in $ppFEV_1$ <5% and 141 had a relative change ≥5%. Baseline characteristics remained well balanced among treatment groups across threshold $ppFEV_1$ categories (Table 1).

As previously reported, treatment with LUM/IVA reduced the rate of PEx vs placebo; the PEx rate ratio was 0.61 for patients who received LUM 400 mg q12h/IVA 250 mg q12h (P<0.001) [17]. Subgroup analyses demonstrated that the reduced PEx rate favored LUM/IVA therapy over placebo irrespective of patient baseline characteristics including $ppFEV_1$, age, sex, medication use, and *Pseudomonas aeruginosa* status (Figure 1).

The relationship between early changes in $ppFEV_1$ and PEx event rate was further evaluated by treatment and threshold category. Overall, patients treated with LUM 400 mg q12h/IVA 250 mg q12h experienced fewer PEx events than patients receiving placebo, regardless of the absolute change in $ppFEV_1$ at day 15 (Figure 2). Although PEx event rates were numerically higher in patients with an absolute change ≤0 than in those with an absolute change >0, no statistically significant differences were observed between the threshold categories (P=0.0556), and LUM/IVA-treated patients in both categories had significantly fewer PEx events compared with those receiving placebo. The rate of PEx leading to IV antibiotics was similar between LUM/IVA-treated patients with early absolute change ≤0 and >0 (0.29 and 0.23 events per year, respectively) and significantly lower in both categories than in patients who received placebo (0.58 events per year). The rate of PEx requiring hospitalization was also similar between LUM/IVA-treated patients with early absolute change ≤0 and >0 (0.18 and 0.17 events per year, respectively) and significantly lower than in placebo-treated patients (0.45 events per year; Figure 2A). Similar findings were observed in patients treated with LUM/IVA compared with placebo, regardless of the early relative change in $ppFEV_1$ from baseline to day 15 of <5% or ≥5% (Figure 2B). Results of the negative binomial regression model confirmed that the absolute change from baseline in $ppFEV_1$ to day 15 was not a predictor of PEx risk (coefficient [95% CI]: 0.00 [−0.03, 0.02]).

Results of exploratory analyses, in which the change in ppFEV$_1$ measured at week 4 and at the average of weeks 16 and 24 was used to categorize treated patients, were generally similar to results reported using the change in ppFEV$_1$ measured at day 15 (Figure S1).

The relationship between early changes in ppFEV$_1$ by treatment and number of days with PEx (normalized for time spent in the study by multiplying the observed percent days with event by the total study days expected [eg, 168 days for 24 weeks]) was also examined. The mean number of days with PEx, days receiving IV antibiotics due to PEx, and days hospitalized for PEx was lower in patients treated with LUM 400 mg q12h/IVA 250 mg q12h than placebo, regardless of the absolute change (≤0 or >0) or relative change in ppFEV$_1$ (<5% or ≥5%) to day 15 (P≤0.0005 vs placebo; Table 2). The mean number of days with PEx for patients with an absolute change ≤0 was approximately twice that in those with an absolute change >0; however, patients in both threshold categories had substantially fewer PEx days compared with those treated with placebo.

Similar findings to those reported with the commercially available dose of LUM/IVA were also observed in patients treated with LUM 600 mg qd/IVA 250 mg q12h. These results are available in the online data supplement (Tables S1 and S2; Figure S2).

4. DISCUSSION

Given the complexity of pathophysiologic changes associated with pulmonary disease progression in individual patients with CF, it is important to consider the totality of clinical outcome measures (eg, lung function, PEx rate, quality of life) when assessing therapeutic benefit in clinical practice. In this subgroup analysis, LUM/IVA-treated patients who did not experience an early increase in lung function, as measured by ppFEV$_1$, had a higher PEx rate and mean number of days with PEx than those with an increase in lung function; however, the treatment benefit in both categories was significant relative to placebo. It is not possible to know for certain whether patients who did not have an early increase in ppFEV$_1$ were at higher risk of PEx than those with an early increase in ppFEV$_1$ due to unidentified factors not measured in the clinical study. Regardless, treated patients included in all categories had fewer PEx than those in the placebo group, and this trend did not exist when looking at the subset of PEx events requiring IV antibiotics or hospitalization. This suggests that the clinical benefits of LUM/IVA therapy extend to patients who did not experience an early increase in lung function. The treatment benefit was also seen in the subset of PEx requiring IV antibiotics and/or hospitalization, where mean number of days with PEx was similar in patients with and without an increase in ppFEV$_1$. These results may assist clinicians in evaluating whether LUM/IVA therapy is beneficial to individual patients.

Potential methodologic limitations exist whereby the outcome variable we are evaluating (PEx) may occur before the stratification variable (ppFEV$_1$), which may lead to overestimation or underestimation of treatment effects. In patients with CF, the interdependence of PEx and ppFEV$_1$ has been established, such that higher lung function is associated with a lower PEx risk and that PEx impacts the rate of lung function decline [6,23,24]. Therefore, we conducted post hoc analyses of PEx outcomes by threshold category using the earliest postbaseline ppFEV$_1$ measure obtained in the studies (ie, day 15)

to limit the number of PEx events that occur before stratification by $ppFEV_1$ and minimize any bias introduced by stratifying in this way. Additional exploratory analyses were performed using threshold categories for change in $ppFEV_1$ measured at week 4 and at the average of weeks 16 and 24. Despite the methodologic shortcomings of these analyses, results were generally similar to the day 15 analyses reported. In addition, a time-varying Cox proportional hazard model of time to first PEx event, with the time-varying covariate being the $ppFEV_1$ measurements over time, was explored, and results were consistent with those reported in the results.

To test whether stratification by >0 and ≤0 was a robust way to assess treated patients, an analysis was conducted in which the quartiles of $ppFEV_1$ changes were used to categorize treated patients into 4 categories. These results were consistent with the results reported above. Pulmonary exacerbation rates for patients receiving placebo varied little across the same quartiles. This justifies the comparison of treated patients' categories with the pooled placebo patients' results.

Prespecified subgroup analyses revealed that reductions in the PEx rate were greater in patients treated with LUM/IVA vs placebo irrespective of patient baseline characteristics. These data indicate that treatment benefits are observed in patients regardless of baseline age, $ppFEV_1$ level, medication use, and *P aeruginosa* status.

CFTR modulators have been shown to impact a multitude of clinical outcomes, including $ppFEV_1$ and PEx [16,17,25]. Results from this post hoc analysis demonstrate the importance of considering the totality of outcomes when evaluating the benefit of CFTR modulators in individual patients. This is especially true considering PEx are clinically meaningful events associated with a progressive loss of lung function, increased risk of future PEx, reduced quality of life, and increased risk of death.

5. CONCLUSIONS

In summary, phase 3 studies of LUM/IVA in patients aged ≥12 years with CF who are homozygous for the *F508del* mutation demonstrated increases in $ppFEV_1$ and reductions in PEx, including PEx requiring IV antibiotics and/or hospitalization; this post hoc analysis showed that PEx were reduced even among patients who did not experience early increases in $ppFEV_1$ in these phase 3 studies. Furthermore, these reductions were observed irrespective of patient baseline characteristics. While measurements of $ppFEV_1$ are critical to assess lung function, these findings also underscore that CFTR modulators confer additional important benefits to treated patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
IV	intravenous
LUM/IVA	lumacaftor/ivacaftor
PEx	pulmonary exacerbations
ppFEV$_1$	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours

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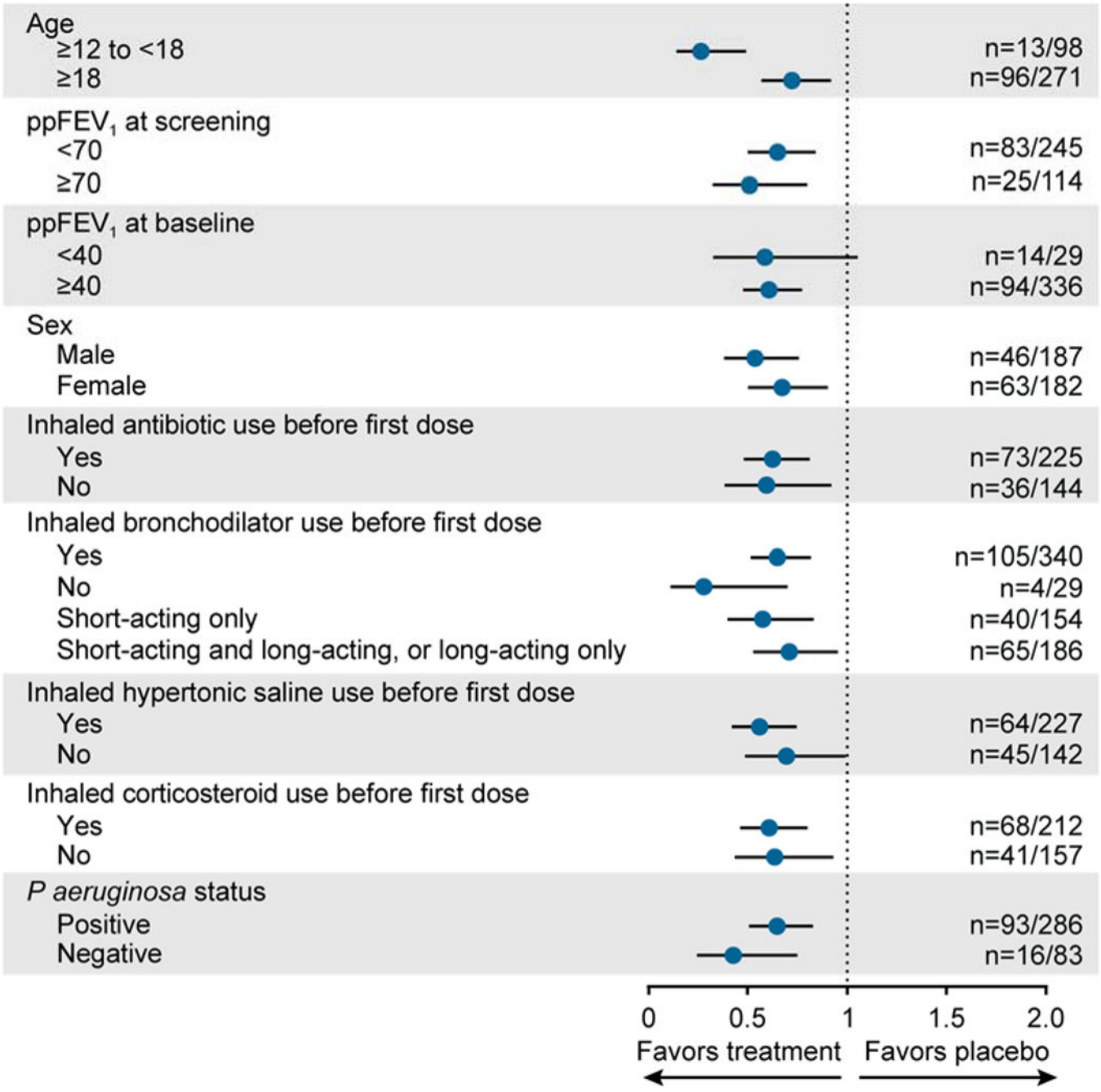
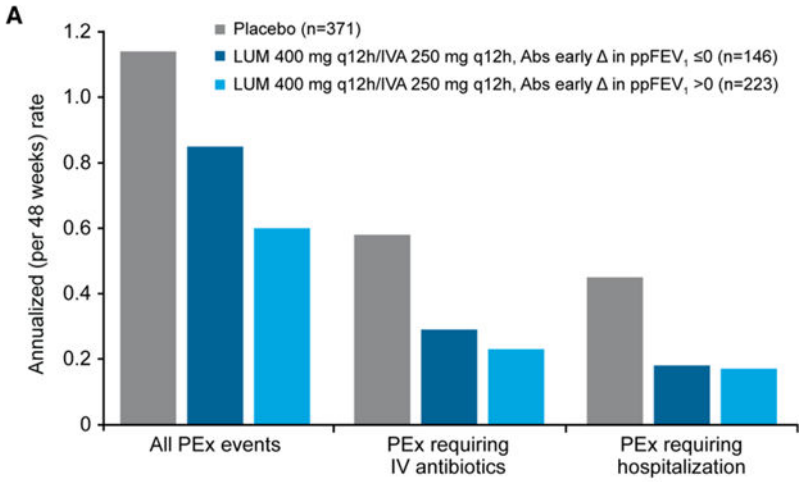
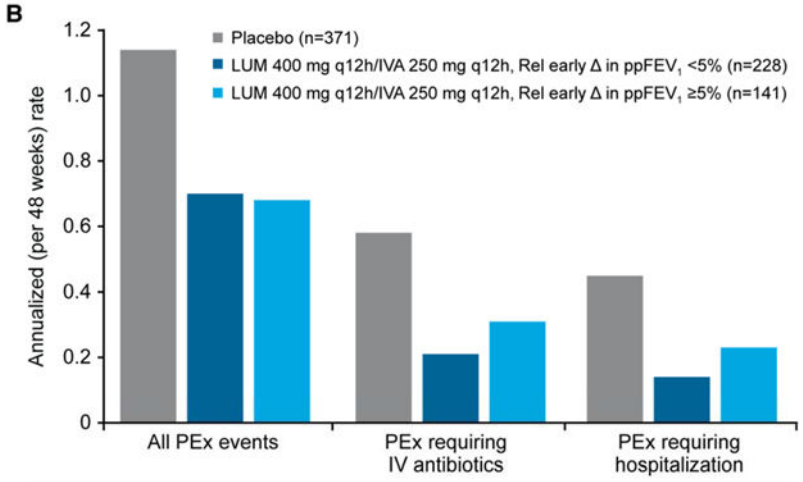


Figure 1.

Subgroup analysis of PEx rate ratio for LUM/IVA vs placebo at week 24. Data shown are rate ratio vs placebo from the pooled TRAFFIC and TRANSPORT studies for patients treated with LUM 400 mg q12h/IVA 250 mg q12h. Error bars represent 95% CIs. IVA, ivacaftor; LUM, lumacaftor; *P aeruginosa*, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.



	Absolute early Δ ≤0	Absolute early Δ >0	Absolute early Δ ≤0	Absolute early Δ >0	Absolute early Δ ≤0	Absolute early Δ >0
Rate ratio vs placebo (95% CI)	0.74 (0.55-0.99)	0.53 (0.40-0.69)	0.49 (0.33-0.74)	0.40 (0.28-0.58)	0.40 (0.23-0.69)	0.38 (0.24-0.59)
P value vs placebo	0.0441	<0.0001	0.0007	<0.0001	0.0009	<0.0001



	Relative early Δ <5%	Relative early Δ ≥5%	Relative early Δ <5%	Relative early Δ ≥5%	Relative early Δ <5%	Relative early Δ ≥5%
Rate ratio vs placebo (95% CI)	0.62 (0.47-0.80)	0.60 (0.44-0.82)	0.37 (0.25-0.54)	0.54 (0.37-0.80)	0.31 (0.19-0.51)	0.50 (0.31-0.82)
P value vs placebo	0.0003	0.0013	<0.0001	0.0020	<0.0001	0.0053

Figure 2.

PEx rates and rate ratios by treatment with LUM 400 mg q12h/IVA 250 mg q12h or placebo and early change in ppFEV$_1$ threshold category. Event rates are described per year by treatment group and ppFEV$_1$ threshold category of the relative change from baseline to day 15 in ppFEV$_1$ of **(A)** ≤0 vs >0 and **(B)** <5% vs ≥5%. Forty-eight weeks was considered equivalent to 1 year for the analysis. Tables show rate ratios (95% CI) for the treatment group vs placebo by ppFEV$_1$ threshold category. Abs Δ, absolute change; IV, intravenous;

IVA, ivacaftor; LUM, lumacaftor; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; Rel Δ, relative change.

Table 1.

Key Baseline Characteristics for Patients Receiving LUM 400 mg q12h/IVA 250 mg q12h or Placebo by Change in ppFEV$_1$ Threshold Category

		LUM 400 mg q12h/IVA 250 mg q12h			
	Placebo (n=371)	**Absolute change ≤0 (n=146)**	**Absolute change >0 (n=223)**	**Relative change <5% (n=228)**	**Relative change ≥5% (n=141)**
Female sex, n (%)	181 (48.8)	73 (50.0)	109 (48.9)	110 (48.2)	72 (51.1)
Age group, n (%), y					
12 to <18	96 (25.9)	34 (23.3)	64 (28.7)	59 (25.9)	39 (27.7)
≥18	275 (74.1)	112 (76.7)	159 (71.3)	169 (74.1)	102 (72.3)
Baseline ppFEV$_1$ subgroup, n (%) *					
<40	28 (7.5)	8 (5.5)	21 (9.4)	13 (5.7)	16 (11.3)
≥40	338 (91.1)	134 (91.8)	202 (90.6)	211 (92.5)	125 (88.7)
Inhaled antibiotic use before first dose, n (%) †	258 (69.5)	90 (61.6)	135 (60.5)	137 (60.1)	88 (62.4)
Inhaled hypertonic saline before first dose, n (%) †	220 (59.3)	89 (61.0)	138 (61.9)	140 (61.4)	87 (61.7)
Use of dornase alfa before first dose, n (%) †	281 (75.7)	107 (73.3)	166 (74.4)	165 (72.4)	108 (76.6)
P aeruginosa positive, n (%)	276 (74.4)	120 (82.2)	166 (74.4)	179 (78.5)	107 (75.9)

IVA, ivacaftor; LUM, lumacaftor; *P aeruginosa*, *Pseudomonas aeruginosa*; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours.

* For patients in whom a ppFEV$_1$ measure was available before the first dose of study drug.

† Includes medication received before the first dose of study drug; patients may or may not have continued to receive the medication at the time the first dose was administered.

Table 2.

Mean Number of Days of PEx by Treatment With LUM 400 mg q12h/IVA 250 mg q12h or Placebo and Change in ppFEV$_1$ Threshold Category *

		LUM 400 mg q12h/IVA 250 mg q12h			
	Placebo (n=371)	**Absolute change ≤0 (n=146)**	**Absolute change >0 (n=223)**	**Relative change <5% (n=228)**	**Relative change ≥5% (n=141)**
Mean days with PEx (SD)	15.7 (24.8)	11.5 (23.1)	5.9 (11.9)	8.9 (19.8)	6.9 (12.6)
P value vs placebo	—	<0.0001	<0.0001	<0.0001	<0.0001
Mean days on IV antibiotics for PEx (SD)	10.1 (20.5)	5.4 (15.8)	2.8 (8.2)	3.8 (13.1)	3.7 (9.5)
P value vs placebo	—	<0.0001	<0.0001	<0.0001	<0.0001
Mean days hospitalized for PEx (SD)	7.6 (18.8)	3.6 (13.7)	1.8 (6.3)	2.6 (11.3)	2.4 (7.2)
P value vs placebo	—	<0.0001	<0.0001	<0.0001	0.0005

IV, intravenous; IVA, ivacaftor; LUM, lumacaftor; PEx, pulmonary exacerbation; ppFEV1, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; SD, standard deviation.

* Change in ppFEV1 from baseline to day 15.