

Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2018

Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR

Jennifer L. Taylor-Cousar
National Jewish Health

Manu Jain
Northwestern University

Tara Lynn Barto
Baylor College of Medicine

Tarik Haddad
Tampa General Hospital

Jeffrey Atkinson
Washington University School of Medicine in St. Louis

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

Recommended Citation

Taylor-Cousar, Jennifer L.; Jain, Manu; Barto, Tara Lynn; Haddad, Tarik; Atkinson, Jeffrey; Tian, Simon; Tang, Rui; Marigowda, Gautham; Waltz, David; Pilewski, Joseph; and VH14-809-106 Investigator Group, "Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for F508del-CFTR." *Journal of Cystic Fibrosis*. 17, 2. 228-235. (2018).
https://digitalcommons.wustl.edu/open_access_pubs/6675

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.

Authors

Jennifer L. Taylor-Cousar, Manu Jain, Tara Lynn Barto, Tarik Haddad, Jeffrey Atkinson, Simon Tian, Rui Tang, Gautham Marigowda, David Waltz, Joseph Pilewski, and VH14-809-106 Investigator Group

Original Article

Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for *F508del-CFTR*☆

Jennifer L. Taylor-Cousar^{a,*}, Manu Jain^b, Tara Lynn Barto^c, Tarik Haddad^d, Jeffrey Atkinson^e, Simon Tian^f, Rui Tang^f, Gautham Marigowda^f, David Waltz^f, Joseph Pilewski^g, on behalf of the VX14-809-106 Investigator Group

^a National Jewish Health, 1400 Jackson St., J318, Denver, CO 80206, USA

^b Feinberg School of Medicine, Northwestern University, 420 E Superior St., Chicago, IL 60611, USA

^c Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA

^d Tampa General Hospital, 1 Tampa General Circle, Tampa, FL 33606, USA

^e Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110, USA

^f Vertex Pharmaceuticals Incorporated, 50 Northern Ave., Boston, MA 02210, USA

^g University of Pittsburgh School of Medicine, 3550 Terrace St., Pittsburgh, PA 15213, USA

Received 13 July 2017; revised 27 September 2017; accepted 28 September 2017

Available online 8 November 2017

Abstract

Objective: Evaluation of the safety, tolerability, and efficacy of lumacaftor/ivacaftor in patients with cystic fibrosis (CF) with severe lung disease. **Methods:** Patients with CF 12 years of age and older, homozygous for *F508del-CFTR*, with percent predicted forced expiratory volume in 1 second (ppFEV₁) < 40 received lumacaftor 400 mg/ivacaftor 250 mg every 12 h (full dose) for 24 weeks in an open-label, prospective study (NCT02390219). Dose modification to half dose for 1–2 weeks (including at initiation) was permitted. Safety and tolerability were the primary outcome measures; clinical outcomes were also assessed.

Results: Of 46 patients (initiated on full dose: n = 28; initiated on half dose: n = 18), 35 (76%) completed 24 weeks of treatment. The most common adverse events included infective pulmonary exacerbation, abnormal respiration, cough, and dyspnea. Compared with patients initiating on full dose, patients initiating at half dose had less frequent respiratory events (56% vs 71%) of shorter median duration (4 vs 9 days). No dose modifications or discontinuations as a result of respiratory events occurred in patients initiating on half dose who were then increased to the full dose over 2 weeks (versus three each for patients on full dose). Following an initial reduction, ppFEV₁ was similar to baseline from week 4 throughout the remainder of the study (least squares mean [95% confidence interval] at week 24: −0.4 [−1.9, 1.1]; p = 0.6249). Compared with the 24 weeks prior to study, the annualized hospitalization rate was lower (rate ratio: 0.41; p = 0.00026) and the duration of intravenous antibiotics was shorter (mean [standard deviation] difference: −8.52 [24.91] days; p = 0.0369) through study week 24.

Conclusions: Compared with patients with higher lung function, respiratory events were more common in patients with ppFEV₁ < 40; aside from these events, the lumacaftor/ivacaftor safety profile was consistent with previous studies. Results suggest that patients with ppFEV₁ < 40 may benefit from treatment initiation at a lower dose with augmented monitoring before increasing to the full dose.

© 2017 The Authors. Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Cystic fibrosis; *F508del*; Lumacaftor; Ivacaftor; Severe lung dysfunction; Advanced lung disease

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CI, confidence interval; IV, intravenous; IVA, ivacaftor; LS, least squares; LUM, lumacaftor; MMRM, mixed-effects model for repeated measures; PEx, pulmonary exacerbations; ppFEV₁, percent predicted forced expiratory volume in 1 s; q12h, once every 12 h; ULN, upper limit of normal.

☆ Funding: This work was supported by Vertex Pharmaceuticals Incorporated.

* Corresponding author.

E-mail address: taylor-cousarj@njhealth.org (J.L. Taylor-Cousar).

<https://doi.org/10.1016/j.jcf.2017.09.012>

1569-1993/© 2017 The Authors. Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

In patients with cystic fibrosis (CF) who were ≥ 12 years of age and homozygous for the *F508del-CFTR* mutation, lumacaftor/ivacaftor (LUM/IVA) combination therapy improved lung function, nutritional status, and pulmonary exacerbations (PE_x) compared with placebo (ClinicalTrials.gov identifiers: NCT01807923 and NCT01807949) [1]. These clinical benefits of LUM/IVA were sustained for up to 120 weeks on treatment and were associated with a reduced rate of decline in percent predicted forced expiratory volume in 1 s (ppFEV₁) compared with the Cystic Fibrosis Foundation registry control population [2].

Compared with patients with higher lung function (ie, ppFEV₁ > 40), patients with CF and advanced lung disease (ppFEV₁ < 40) have a greater burden of disease, with an increased frequency of PE_x, worse nutritional status, a greater likelihood of lung transplantation, and an increased risk of mortality [3–6]. Assessing therapeutic options that are both safe and effective is of particular interest for patients with CF and advanced lung disease.

While the eligibility criteria to enroll in LUM/IVA pivotal clinical studies required patients to have a ppFEV₁ of 40–90 at screening [1], a subgroup analysis of phase 3 LUM/IVA clinical studies examined the safety and efficacy of LUM/IVA in patients whose ppFEV₁ fell below 40 between the screening and baseline study visits [7]. Treatment benefits in patient with ppFEV₁ < 40 were consistent with the overall patient population; however, an increased incidence of respiratory events, including dyspnea and chest tightness, were observed [7]. In the clinical practice setting, there have been reports of increased frequency in respiratory adverse events (AEs) in patients with ppFEV₁ < 40 initiating treatment with LUM/IVA [8–10]. This study evaluated the safety and efficacy of LUM/IVA in patients with CF who were homozygous for the *F508del-CFTR* mutation and had advanced lung disease (ppFEV₁ < 40) in a prospective, open-label, 24-week clinical study.

2. Methods

This was a phase 3b open-label study of LUM/IVA (Orkambi, Vertex Pharmaceuticals Incorporated, Boston, MA, USA) in patients with CF who were homozygous for the *F508del-CFTR* mutation and had advanced lung disease (ppFEV₁ < 40) (ClinicalTrials.gov identifier: NCT02390219). The study was conducted in accordance with Good Clinical Practice guidelines and was reviewed and approved by institutional review boards. All patients of age of consent (per local requirements) provided written informed consent; for patients below the local age of consent, the patient's parent/legal guardian provided written informed consent, and the patient provided assent when applicable per local requirements.

This study was conducted at six sites in the United States between February 19, 2015, and October 3, 2016. Eligible patients with a diagnosis of CF were 12 years of age or older, homozygous for the *F508del-CFTR* mutation, and had a ppFEV₁ value < 40 adjusted for age, gender, and height at screening [11,12] (ppFEV₁ ≥ 40 at baseline was permitted). Key exclusion criteria included (1) current use of invasive mechanical

ventilation; (2) a history of any significant comorbidity or laboratory abnormality that, in the investigator's judgment, might have interfered with study assessments or posed an undue risk for the patient; and (3) abnormal liver (at least 3 of aspartate aminotransferase [AST], alanine aminotransferase (ALT), gamma-glutamyl transpeptidase, and alkaline phosphatase ≥ 3 times the upper limit of normal (ULN); or ALT or AST > 5 times ULN; or bilirubin > 2 times ULN) or renal function (glomerular filtration rate ≤ 45 ml/min/1.73 m², calculated by the Counahan-Barratt equation [13]). Target enrollment was 100 to 200 patients.

Patients received LUM 400 mg every 12 h (q12h) in combination with IVA 250 mg q12h orally for 24 weeks. Based on the observation early in this study of a serious AE of respiratory chest tightness, the study protocol was amended to permit the option of modification to half dose of study drug (LUM 200 mg q12h in combination with IVA 125 q12h) for up to 7 days at the discretion of the treating physician following discussion with and approval by the medical monitor. This included the option of initiating the study on half dose of study drug. The dose modification could be extended by the treating physician; no patient was on the modified dose for > 15 days.

Patient visits were as follows: screening (within 4 weeks of study initiation), days 1 and 2, weeks 2, 4, 8, 16, and 24, and follow-up 4 weeks after the last dose of study drug (Fig. 1). Spirometry was performed at all patient visits and the Cystic Fibrosis Questionnaire–Revised (CFQ-R), weight, height, pregnancy test, vital signs, pulse oximetry, and information on AEs and concomitant medications, treatments, and procedures were collected at all study visits. All questionnaires were completed before the start of any other assessments scheduled at that visit. In addition, telephone interviews were conducted at day 3, week 12, and week 20 to assess patients' status, any AEs, concomitant medications, treatments, and procedures.

2.1. Outcomes

The primary endpoint was the safety and tolerability of LUM/IVA based on treatment-emergent AEs (Medical Dictionary for Regulatory Activities [MedDRA] version 19), including respiratory adverse events of special interest (AESIs; defined as asthma, bronchial hyperreactivity, bronchospasm, chest discomfort, dyspnea, respiration abnormal, and wheezing), clinical laboratory values (hematology and serum chemistry), and standard digital 12-lead electrocardiograms. Safety evaluations also included physical examinations, vital signs (including nutritional status parameters), pulse oximetry, and day 2 spirometry. Secondary endpoints included absolute change from baseline in ppFEV₁ at each study visit up to week 24, absolute change from baseline in the CFQ-R respiratory domain score through week 24, absolute change from baseline in sweat chloride to the average of day 15 and week 4, total number of days of intravenous (IV) antibiotics for sinopulmonary signs and symptoms through week 24, and total number of all-cause hospitalizations through week 24. Absolute change from baseline in body mass index (BMI) was evaluated as an additional safety assessment and was also evaluated for efficacy.

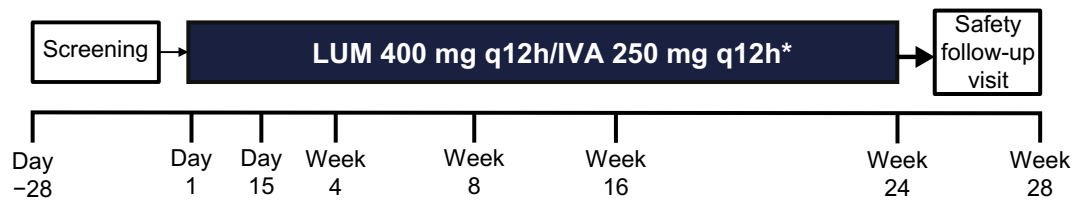


Fig. 1. Study design. IVA, ivacaftor; LUM, lumacaftor; q12h, every 12 h. *Dose modification to LUM 200 mg q12h/IVA 125 mg q12h (half dose) was permitted (at initiation or at any point during the study) at the discretion of the treating physician and after discussion with and approval by the medical monitor.

2.2. Statistical analysis

Safety was assessed in all patients who received ≥ 1 dose of study drug and was analyzed using descriptive statistics. No formal sample size calculations were performed. Absolute change from baseline in ppFEV₁ was analyzed based on a mixed-effects model for repeated measures (MMRM) for all patients who received study drug. The MMRM included absolute change from baseline in ppFEV₁ as the dependent variable, visit as a fixed effect, and subject as a random effect, with adjustment for gender and baseline ppFEV₁ as a continuous variable. Absolute change from baseline in the CFQ-R respiratory domain score and sweat chloride was analyzed using a similar model, with baseline ppFEV₁ replaced in the model by baseline CFQ-R score and sweat chloride, respectively. A mixed-effects model was used for analysis and was based on restricted maximum likelihood estimation and assuming that conditional on fixed and random effects, data were missing at random, and no imputation of missing data were done. An additional analysis of BMI was performed using descriptive statistics.

The total number of days of IV antibiotics for sinopulmonary signs and symptoms through week 24 was normalized for time spent in the study by calculating the percentage of days

with IV antibiotics multiplied by 168 (ie, the total study days expected through week 24). This number was compared with the normalized total number of days in the 24 weeks prior to study entry (collected retrospectively) using a paired sample *t*-test. Normality was evaluated using a Shapiro–Wilk test assuming a 0.05 level of significance. A Wilcoxon signed-rank test was prespecified if the normality assumption was violated. The number of all-cause hospitalizations through week 24 was compared with the number in the 24 weeks prior to study entry (collected retrospectively) and analyzed similarly to total days with IV antibiotics. An additional analysis was performed to directly compare calculated event rates, assuming a Poisson distribution of the number of events in each period (ie, the 24-week study period versus 24 weeks prior to study entry).

3. Results

Forty-six patients enrolled in the study and received at least one dose of study drug; this was lower than the target enrollment of 100 to 200 patients and was likely a consequence of commercial drug availability. Baseline demographics and clinical characteristics are shown in Table 1. The mean (min, max) patient age was 32.1 (17, 56) years, ppFEV₁ was 29.1 (18.3, 42.0), and BMI was 21.41 (15.65, 28.50) kg/m². The

Table 1
Baseline demographics and characteristics.

Characteristic	LUM 200 mg q12h/IVA 125 mg q12h ^a (N = 18)	LUM 400 mg q12h/IVA 250 mg q12h (N = 28)	LUM/IVA (N = 46)
Male, n (%)	11 (61)	19 (68)	30 (65)
Age, mean (min, max), y	32.9 (17, 56)	31.6 (18, 56)	32.1 (17, 56)
Age groups, n (%), y			
<18	1 (6)	0 (0)	1 (2)
≥ 18	17 (94)	28 (100)	45 (98)
ppFEV ₁ , mean (min, max)	26.9 (18.4, 42.0)	30.6 (18.3, 37.1)	29.1 (18.3, 42.0)
BMI, mean (min, max), kg/m ²	20.9 (15.7, 26.1)	21.7 (17.1, 28.5)	21.4 (15.7, 28.5)
Chronic medications, n (%) ^b			
Dornase alfa	16 (89)	22 (79)	38 (83)
Any inhaled antibiotic	16 (89)	23 (82)	39 (85)
Any inhaled bronchodilator	18 (100)	27 (96)	45 (98)
Any inhaled hypertonic saline	14 (78)	22 (79)	36 (78)
Documented on lung transplant waiting list at screening, n (% of patients with available information)			
Yes	1 (25)	1 (4)	2 (7)
No	3 (75)	22 (96)	25 (93)
Information not available	14	5	19

BMI, body mass index; IVA, ivacaftor; LUM, lumacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 s.

^a Patients who initiated at the modified dose for 1–2 weeks and then increased to the full dose.

^b Includes medications received before the first dose of study drug; medications may or may not have continued at the time of first dose.

Table 2
Summary of AEs.

	LUM/IVA (N = 46) n (%)
Any AE	43 (93)
AE leading to treatment interruption	7 (15)
AE leading to dose modification	5 (11)
AE leading to treatment discontinuation	8 (17)
Serious AE	18 (39)
AE leading to death	1 (2)
AE with incidence ≥10%	
Infective PEx of CF	27 (59)
Respiration abnormal	26 (57)
Cough	21 (46)
Dyspnea	20 (43)
Sputum increased	13 (28)
Oropharyngeal pain	9 (20)
Hemoptysis	8 (17)
Fatigue	7 (15)
Headache	7 (15)
Decreased appetite	5 (11)
Diarrhea	5 (11)
Nasal congestion	5 (11)
Nausea	5 (11)
Wheezing	5 (11)

AEs were treatment-emergent events and did not necessarily have a causal relationship with study drug. A patient with multiple events within a category was counted only once in that category.

AE, adverse event; CF, cystic fibrosis; IVA, ivacaftor; LUM, lumacaftor; PEx, pulmonary exacerbation.

most common concomitant medications were as expected for a population with CF with severe lung dysfunction [14]. Of the 46 patients, 35 (76%) completed treatment with LUM/IVA through 24 weeks, and 11 (24%) discontinued treatment. AEs were the most common reason for treatment discontinuation ($n = 8$; 17%); one patient refused further dosing, 1 patient was lost to follow-up, and 1 patient was ineligible. The most common AEs that led to treatment discontinuation were respiration abnormal ($n = 3$) and dyspnea ($n = 2$).

Table 3
Summary of respiratory AESIs.

	LUM 200 mg q12h/IVA 125 mg q12h ^a (N = 18)	LUM 400 mg q12h/IVA 250 mg q12h (N = 28)	LUM/IVA Overall (N = 46)
Respiratory AESIs, n (%) ^b	10 (56)	20 (71)	30 (65)
Dyspnea	6 (33)	14 (50)	20 (43)
Abnormal respiration	9 (50)	17 (61)	26 (57)
Asthma	1 (6)	0 (0)	1 (2)
Wheezing	1 (6)	4 (14)	5 (11)
Duration of events, median (min, max), days	4.0 (1, 55)	9.0 (1, 61)	9.0 (1, 61)
Time to onset of first event, median (min, max), days	1.0 (1, 8)	1.0 (1, 5)	1.0 (1, 8)
Patients with events leading to dose modification, n (%)	0 (0)	3 (11)	3 (7)
Patients with events leading to treatment discontinuation, n (%)	0 (0)	3 (11)	3 (7)
Serious events, n (%)	0 (0)	1 (4)	1 (2)
Treatment-related serious events, n (%)	0 (0)	1 (4) ^c	1 (2) ^c

A patient with multiple events within a category was counted only once in that category. AE, adverse event; AESI, adverse event of special interest; IVA, ivacaftor; LUM, lumacaftor; q12h, once every 12 h.

^a Patients who initiated at the modified dose for 1 to 2 weeks and then increased to the full dose.

^b Bronchial hyperreactivity, bronchospasm, and chest discomfort were not reported in any patients.

^c Treatment-related serious respiratory AESI was respiration abnormal.

A total of 28 patients (61%) received a starting dose of LUM 400 mg q12h/IVA 250 mg q12h (full dose), and 18 (39%) received an initial dose of LUM 200 mg q12h/IVA 125 mg q12h (half dose) for 1–2 weeks followed by escalation to the full dose. Overall, baseline characteristics were similar between patients who initiated full-dose LUM/IVA treatment and those initiated on half dose LUM/IVA (Table 1). The mean (min, max) ppFEV₁ was 26.9 (18.4, 42.0) for patients who started on the half dose of LUM/IVA and 30.6 (18.3, 37.1) for patients who started on the full dose.

A summary of AEs is shown in Table 2. The most frequently reported AEs were infective PEx of CF (59%), abnormal respiration (57%), cough (46%), dyspnea (43%), increased sputum (28%), oropharyngeal pain (20%), hemoptysis (17%), fatigue (15%), headache (15%), decreased appetite (11%), diarrhea (11%), nasal congestion (11%), nausea (11%), and wheezing (11%).

Respiratory AESIs for the overall study population and by treatment initiation dose are shown in Table 3. Overall, the incidence of respiratory AESIs was 65%, and these events had an early onset (median [min, max]: 1 [1, 8] days). Of note, a lower incidence and shorter duration of respiratory AESIs occurred in patients initiated on half-dose LUM/IVA than in those initiated on full-dose LUM/IVA (56% vs 71% incidence; median [min, max] duration of 4.0 [1, 55] days vs 9.0 [1, 61] days) (Table 3).

Five patients had AEs that necessitated dose reduction (events leading to dose reduction in >1 patient: respiration abnormal, $n = 3$ [7%]; cough, $n = 2$ [4%]; dyspnea $n = 2$ [4%]; some patients underwent dose reduction due to multiple AEs). Seven patients had AEs that necessitated temporary dose interruption; infective pulmonary exacerbation was the only AE that led to treatment interruption in >1 patient ($n = 2$). No dose modifications or discontinuations due to respiratory AESIs were required in patients initiating on half dose of LUM/IVA. In comparison, among patients initiated on full-dose LUM/IVA, there were three dose modifications and three discontinuations.

Overall, no clinically meaningful changes or trends were observed in clinical laboratory values (hematology and serum chemistry), electrocardiograms, or vital signs, and no safety signals were observed in review of spirometry data.

One 33-year-old male patient died following a serious AE of hemoptysis. The patient received study drug from days 1 to 4, discontinued treatment from day 4 due to respiratory chest tightness, and permanently discontinued due to increased shortness of breath and respiratory chest tightness. Both AEs were deemed related to study drug by the investigator and resolved on day 8. The serious AE of hemoptysis occurred 12 days after the last dose of study drug (study day 16), and the investigator deemed it unlikely to be treatment related.

Five patients (11%) had an ALT or AST elevation >3 times the upper limit of normal (ULN), including three patients (7%) who had an ALT or AST elevation >5 times the ULN. One patient had an AST elevation >3 times the ULN concurrent with a total bilirubin elevation >2 times the ULN that was observed at the safety follow-up visit. At screening, all five of these patients had ALT and AST <3 times the ULN and bilirubin <1.5 times the ULN. The patient had a history of increased hepatic enzymes and bile duct stone and cholecystectomy. Transaminase elevations were noted at screening and baseline,

and bilirubin was elevated at baseline. The patient permanently discontinued LUM/IVA after 11 days due to chest pain, fatigue, dyspnea, and abnormal respiration; these events were deemed possibly related to study drug. No dose modifications or discontinuations occurred due to elevated transaminases.

There was an initial decrease from baseline in mean absolute ppFEV₁ (least squares [LS] mean change [95% CI] at day 15: −1.7 [−3.2, −0.1] percentage points; $p = 0.0332$); ppFEV₁ returned to baseline at the week 4 study visit and remained near baseline through week 24 (LS mean [95% CI] at week 24: −0.4 [−1.9, 1.1]; $p = 0.6249$) (Fig. 2A). An increase from baseline in the mean absolute CFQ-R respiratory domain score through week 24 was seen (LS mean change [95% CI]: 2.5 [−1.0, 5.9] points) that did not reach statistical significance ($p = 0.1554$) (Fig. 2B). Treatment with LUM/IVA resulted in a rapid and sustained significant reduction in sweat chloride concentration. The LS mean (95% CI) absolute change from baseline at the average of day 15 and week 4 was −16.4 (−19.2, −13.7) mmol/L ($p < 0.0001$) and at week 24 was −20.2 (−24.3, −16.1) mmol/L ($p < 0.0001$) (Fig. 2C). Change from baseline in BMI showed an initial decrease at day 15 (mean [standard error of the mean]: −0.16 [0.06] kg/m²) followed by an increase over 24 weeks of treatment. An increase in BMI was observed by week 16 (0.17

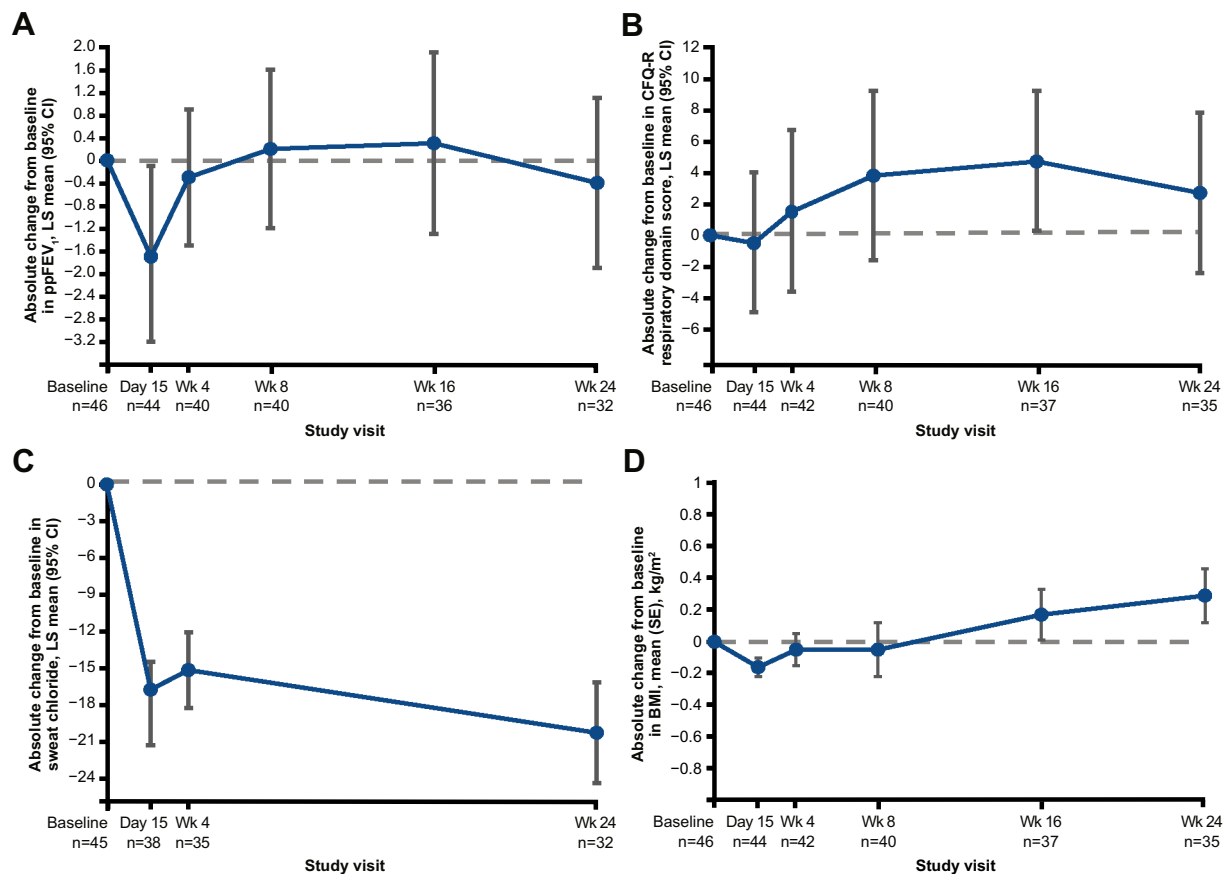


Fig. 2. Absolute change from baseline in (A) ppFEV₁, (B) CFQ-R respiratory domain score, (C) sweat chloride, and (D) BMI at each study visit. Panels A–C are based on MMRM analysis, and panel D is based on descriptive statistics. The number of patients is noted below each corresponding study visit. BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CI, confidence interval; LS, least squares; MMRM, mixed-effects model for repeated measures; ppFEV₁, percent predicted forced expiratory volume in 1 s; SE, standard error.

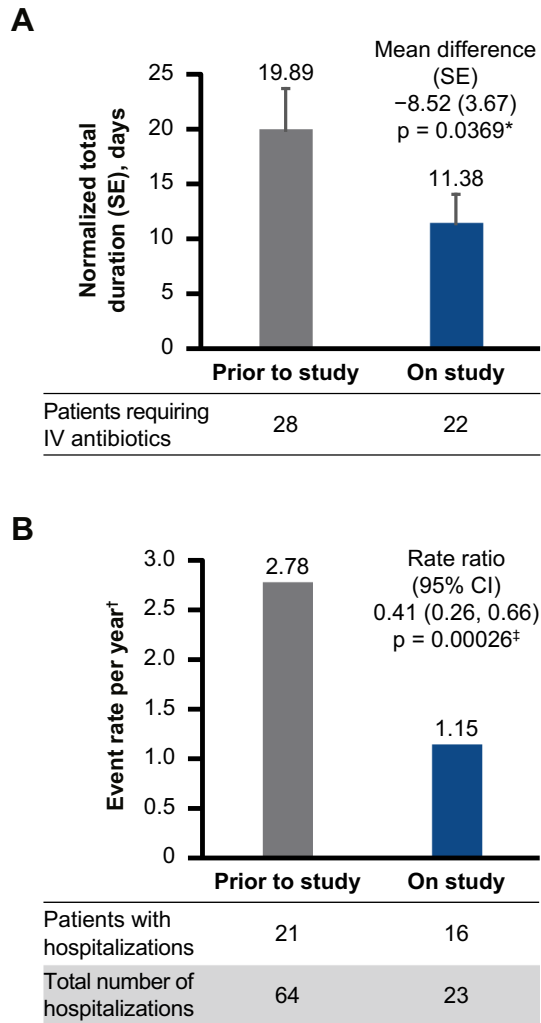


Fig. 3. (A) Total duration of IV antibiotics for sinopulmonary signs and symptoms and (B) annualized all-cause hospitalization event rate in the 24 weeks prior to the study and through 24 weeks on study drug ($N = 46$). *Wilcoxon signed-rank test. †Number of hospitalizations divided by the total number of days during the period was used to calculate event rate; annualized event rate (ie, event rate per year) was derived by multiplying the event rate by 48 weeks (7 days/week). ‡A Poisson distribution of the number of events on each period was assumed. The log of rate ratio thus approximated the normal distribution. The definition of hospitalization pre-study may not be the same as protocol-defined hospitalization. The p value was for testing the null hypothesis that the log of rate ratio = 0. CI, confidence interval; IV, intravenous; SE, standard error.

[0.16] kg/m²), along with a further increase at week 24 (0.29 [0.17] kg/m²) (Fig. 2D), and BMI remained higher than baseline at the follow-up visit (0.10 [0.21] kg/m²).

A shorter duration of IV antibiotics and a lower annualized hospitalization rate were observed during the 24-week treatment period than in the 24 weeks prior to the study. The mean normalized duration of IV antibiotics through 24 weeks on study drug was 11.38 days, significantly less than the mean of 19.89 days in the 24 weeks prior to the study (mean difference [standard error]: -8.52 [3.67]; $p = 0.0369$) (Fig. 3A). The number of hospitalizations was lower through week 24 on study than in the 24 weeks prior to study initiation (23

hospitalizations in 16 patients vs 64 hospitalizations in 21 patients; Wilcoxon signed-rank test, $p = 0.0002$). The estimated annualized event rate through 24 weeks on study drug (1.15 events/year) was also lower than in the 24 weeks prior to study initiation (2.78 events/year; $p = 0.00026$) (Fig. 3B).

4. Discussion

In this open-label 24-week study, the safety profile of LUM/IVA in patients with CF and advanced lung disease who were homozygous for *F508del-CFTR* was generally consistent with previous clinical studies of LUM/IVA, and the most frequently observed AEs are common manifestations of CF (except for oropharyngeal pain) [15]. However, respiratory events were more frequently reported than in studies that enrolled patients with ppFEV₁ > 40 at baseline [1,2]. Consistent with previous reports [1,2], respiratory events reported in this study were largely associated with treatment initiation.

The frequency of respiratory-related events was greater than that observed in a subgroup analysis of phase 3 LUM/IVA studies examining patients whose ppFEV₁ fell to <40 between screening and baseline [7], although that study encompassed a different patient population, namely, patients with ppFEV₁ > 40 at screening. Indeed, differences suggest that the subgroup analyzed from previous phase 3 studies (ppFEV₁ falling below 40 after baseline) included patients with less advanced lung disease, which was reflected in their higher baseline ppFEV₁ (mean ppFEV₁ of 37.2 in the LUM/IVA subgroup vs 29.1 in the present study) [7]. Moreover, in these subgroup analyses by Elborn et al., fewer patients with ppFEV₁ ≥ 40 at baseline had respiratory events (dyspnea) than did those with ppFEV₁ that fell below 40 at baseline. The rates of respiratory events observed here were lower than those from a recent report in patients with CF and advanced lung disease who initiated LUM/IVA in real-world clinical practice [10]. Popowicz et al. reported respiratory events within 24 h of LUM/IVA initiation in 83% of patients (but 66% at 1 month) as well as acute deterioration in ppFEV₁ (median change [interquartile range] at 2 h post initiation, -19 [-21 to -11] percentage points) [10]. Hubert et al. reported a respiratory event rate of 51% in patients with CF and advanced lung disease initiating LUM/IVA, with ppFEV₁ improvements over 3 months of treatment comparable to those observed in the phase 3 studies [1,8]. The differences in respiratory events in these reports and the current study may be due to differences in the populations, reporting systems, and/or disease characteristics assessed.

In a retrospective chart review of patients receiving LUM/IVA, higher rates of respiratory events were observed compared with rates observed in LUM/IVA clinical trials in the subgroup of patients with advanced lung disease, although treatment was reported to be initiated at a lower dose in such patients (dose not specified) [9]. The majority of patients in the Popowicz et al. and Hubert et al. studies were initiated on full-dose therapy [8,10]. In the present study, some patients were initiated at a modified dose (LUM 200 mg q12 h/IVA 125 mg q12h [half-dose therapy]). The dose modification permitted in this study was implemented because the incidence

of respiratory AEs (eg, dyspnea and shortness of breath) was noted to be dose dependent in phase 2 studies evaluating LUM/IVA combination therapy during the LUM monotherapy phase [16]. This lower initiation dose was associated with a decreased rate of respiratory events and no treatment discontinuations due to respiratory events despite patients having a somewhat lower mean ppFEV₁ at baseline than patients who started treatment on full dose (LUM 400 mg q12h/IVA 250 mg q12h). In the current study, overall rates of treatment discontinuation due to any AE in patients with ppFEV₁ < 40 (8 of 46 patients [17%]) were lower than those observed in the aforementioned retrospective analyses (25%–32%) [8–10]. It should be noted that patients enrolled in this prospective trial may have had higher compliance and a greater willingness to persist with treatment rather than to discontinue following adverse events versus patients included in the prior retrospective studies; this adherence is to be expected when comparing real-world retrospective studies with prospective clinical trials.

While this study was not powered to assess efficacy, LUM/IVA was associated with reductions in the duration of IV antibiotics for exacerbation-related symptoms and in the number of all-cause hospitalizations. As exacerbations are associated with a decrease in quality of life [17,18], increased risk of future exacerbations [19,20], and mortality [21], these data provide evidence for a potential treatment benefit in this patient population. Treatment with LUM/IVA was also associated with an increased BMI over the course of 24 weeks, indicating an amelioration in nutritional status in these patients with CF with advanced lung disease. Furthermore, this BMI improvement could make patients with advanced lung disease more desirable transplant candidates. Although there were no improvements in ppFEV₁ over the course of this study, lung function generally remained near baseline. A modest change in ppFEV₁ (−1.7 percentage points) was observed early in the course of treatment (day 15). Lung function recovered by the next study visit and remained near baseline over the 24-week study period. Decreased sweat chloride following LUM/IVA treatment further supports the effect of CFTR modulation in these patients.

The open-label design as well as lack of a direct comparison to patients with higher lung function (ppFEV₁ > 40) limits interpretation of these findings. As this was primarily a safety study for this group of patients who were not eligible for enrollment in the phase III trials for safety reasons, no control group was included. This design limits the efficacy analyses to within-group comparisons versus baseline measurements. Another limitation of this study is the lower-than-projected patient enrollment, which is partly explained by patients having had the option of receiving treatment with marketed LUM/IVA following its rapid US Food and Drug Administration approval rather than receiving treatment through study enrollment. However, these data remain informative for this population of patients with CF with advanced lung disease, who have infrequently been assessed. Finally, we note that in analyses showing reductions in the duration of IV antibiotics and total number of hospitalizations, comparisons may have been

confounded by differences in data collected during the 24 weeks on study and data collected retrospectively for the 24 weeks before the study. Additional observational studies to prospectively evaluate exacerbation-related outcomes may be warranted to confirm these findings.

In summary, in patients with CF and advanced lung disease with ppFEV₁ < 40, the incidence of respiratory events was higher than that previously observed in patients with less severe lung dysfunction [1,2,7]. However, the safety profile of LUM/IVA was generally consistent with the established safety profile of this CFTR modulator combination, and with the AEs expected in patients with this degree of lung dysfunction. Reductions in IV antibiotics for exacerbation-related symptoms and all-cause hospitalizations were observed and provide evidence for a potential treatment benefit. Dose modification using half-dose LUM/IVA before escalating to the full dose was associated with fewer respiratory events and no treatment discontinuations, suggesting that patients with ppFEV₁ < 40 may benefit from treatment initiation at a lower dose with augmented monitoring before subsequent increase to the full dose.

Author contributions

The authors collaborated with the study sponsor (Vertex Pharmaceuticals Incorporated) on the study design and statistical analysis plan. **RT** performed the analysis. **JLTC**, **MJ JA**, **GM**, and **JP** contributed to the conception and initial drafting of the manuscript, with input from all authors. All authors had full access to the study data, contributed to the interpretation of the data, participated in revisions, and approved the decision to submit for publication.

Role of the funding source

The sponsor participated in the design of the protocol in collaboration with the authors. The sponsor performed the statistical analysis and contributed to data interpretation. Medical writing and editorial support and coordination were funded by the sponsor.

Declaration of interests

JLTC has received fees for advisory board participation and her institution has received grant funding from Vertex Pharmaceuticals Incorporated. **MJ** has received fees for advisory board participation and his institution has received grant funding from Vertex Pharmaceuticals Incorporated. **TLB** has received fees for advisory board participation from Vertex Pharmaceuticals Incorporated. **TH** has received fees for physician oversight in clinical trials from Vertex Pharmaceuticals Incorporated. **JA** has received payment for clinical trial involvement from Vertex Pharmaceuticals Incorporated. **ST**, **RT**, **GM**, and **DW** are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. **JP** has received fees for an advisory board and his institution has received grant funding from Vertex Pharmaceuticals Incorporated.

Acknowledgments

We thank all the patients, coordinators, and investigators who participated in this study.

Medical writing and editorial support were provided by Scott Bayer, PhD, Thomas Pickette, PharmD, MBA, Michelle Yochum, PhD, Dena McWain, and Joshua Safran. **SB** and **TP** are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. **MY**, **DM**, and **JS** are employees of Ashfield Healthcare Communications, which received funding from Vertex Pharmaceuticals Incorporated.

References

- [1] Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015;373:220–31.
- [2] Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017;5:107–18.
- [3] Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: epidemiology and pathogenesis. *Thorax* 2007;62:360–7.
- [4] Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326:1187–91.
- [5] Ramos KJ, Quon BS, Heltshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, et al. Heterogeneity in survival in adult patients with cystic fibrosis with FEV1 <30% of predicted in the United States. *Chest* 2017;151:1320–8.
- [6] Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. *Thorax* 2002;57:596–601.
- [7] Elborn JS, Ramsey BW, Boyle MP, Konstan MW, Huang X, Marigowda G, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *Lancet Respir Med* 2016;4:617–26.
- [8] Hubert D, Chiron R, Camara B, Grenet D, Prevotat A, Bassinet L, et al. Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease. *J Cyst Fibros* 2017;16:388–91.
- [9] Jennings MT, Dezube R, Paranjape S, West NE, Hong G, Braun A, et al. An observational study of outcomes and tolerances in patients with cystic fibrosis initiated on lumacaftor/ivacaftor. *Ann Am Thorac Soc* Apr 13 2017 [Epub ahead of print].
- [10] Popowicz N, Wood J, Tai A, Morey S, Mulrennan S. Immediate effects of lumacaftor/ivacaftor administration on lung function in patients with severe cystic fibrosis lung disease. *J Cyst Fibros* 2017;16:392–4.
- [11] Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–87.
- [12] Wang X, Dockery DW, Wypij D, Fay ME, Ferris Jr BG. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993;15:75–88.
- [13] Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM. Estimation of glomerular filtration rate from plasma creatinine concentration in children. *Arch Dis Child* 1976;51:875–8.
- [14] Mogayzel Jr PJ, Naureckas ET, Robinson KA, Mueller G, Hadjilias D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2013;187:680–9.
- [15] Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med* 2003;168:918–51.
- [16] Boyle MP, Bell SC, Konstan MW, McColley SA, Rowe SM, Rietschel E, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *Lancet Respir Med* 2014;2:527–38.
- [17] Bradley JM, Blume SW, Balp MM, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. *Eur Respir J* 2013;41:571–7.
- [18] 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;121:64–72.
- [19] VanDevanter DR, Morris NJ, Konstan MW. IV-treated pulmonary exacerbations in the prior year: an important independent risk factor for future pulmonary exacerbation in cystic fibrosis. *J Cyst Fibros* 2016;15:372–9.
- [20] VanDevanter DR, Pasta DJ, Konstan MW. Treatment and demographic factors affecting time to next pulmonary exacerbation in cystic fibrosis. *J Cyst Fibros* 2015;14:763–9.
- [21] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;153:345–52.