ORIGINAL ARTICLE

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

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ABSTRACT

BACKGROUND

Cystic fibrosis is a life-limiting disease that is caused by defective or deficient cystic fibrosis transmembrane conductance regulator (CFTR) protein activity. Phe508del is the most common *CFTR* mutation.

METHODS

We conducted two phase 3, randomized, double-blind, placebo-controlled studies that were designed to assess the effects of lumacaftor (VX-809), a CFTR corrector, in combination with ivacaftor (VX-770), a CFTR potentiator, in patients 12 years of age or older who had cystic fibrosis and were homozygous for the Phe508del *CFTR* mutation. In both studies, patients were randomly assigned to receive either lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) or matched placebo for 24 weeks. The primary end point was the absolute change from baseline in the percentage of predicted forced expiratory volume in 1 second (FEV_1) at week 24.

RESULTS

A total of 1108 patients underwent randomization and received study drug. The mean baseline FEV_1 was 61% of the predicted value. In both studies, there were significant improvements in the primary end point in both lumacaftor–ivacaftor dose groups; the difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV_1 ranged from 2.6 to 4.0 percentage points ($P<0.001$), which corresponded to a mean relative treatment difference of 4.3 to 6.7% ($P<0.001$). Pooled analyses showed that the rate of pulmonary exacerbations was 30 to 39% lower in the lumacaftor–ivacaftor groups than in the placebo group; the rate of events leading to hospitalization or the use of intravenous antibiotics was lower in the lumacaftor–ivacaftor groups as well. The incidence of adverse events was generally similar in the lumacaftor–ivacaftor and placebo groups. The rate of discontinuation due to an adverse event was 4.2% among patients who received lumacaftor–ivacaftor versus 1.6% among those who received placebo.

CONCLUSIONS

These data show that lumacaftor in combination with ivacaftor provided a benefit for patients with cystic fibrosis homozygous for the Phe508del *CFTR* mutation. (Funded by Vertex Pharmaceuticals and others; TRAFFIC and TRANSPORT ClinicalTrials.gov numbers, NCT01807923 and NCT01807949.)

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*A complete list of the investigators in the TRAFFIC and TRANSPORT studies is provided in the Supplementary Appendix, available at NEJM.org.

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Cystic fibrosis is a genetic disease that is associated with high rates of premature death.[1-4] It is a multisystem disease that is characterized by pancreatic insufficiency and chronic airway infections associated with loss of lung function, repeated pulmonary exacerbations, and, ultimately, respiratory failure.[5]

Cystic fibrosis is caused by gene mutations that result in deficient or dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein, an anion channel that is normally present in the epithelial membrane. Phe508del (c.1521_1523delCTT; formerly F508del) is the most common *CFTR* mutation; approximately 45% of patients with cystic fibrosis are homozygous for this allele.[1] Cystic fibrosis is a progressive disease; despite advances in therapies designed to address the symptoms of the disease, the median predicted survival among patients who are homozygous for Phe508del in the United States is 37 years.[6] The Phe508del *CFTR* mutation causes a processing defect that severely reduces protein levels at the epithelial membrane; for the few channels that reach the cell surface, the mutation also disrupts channel opening; together, these effects lead to minimal CFTR chloride transport activity.[7-10] One approach to treating cystic fibrosis is to address the underlying cause of the disease by targeting the CFTR protein dysfunction. Restoring chloride transport to p.Phe508del CFTR (formerly F508del CFTR) is therefore thought to require at least two steps: correction of cellular misprocessing to increase the amount of functional mutated CFTR and potentiation to further increase channel opening.

Lumacaftor is an investigational CFTR corrector that has been shown in vitro to correct p.Phe508del CFTR misprocessing and increase the amount of cell surface–localized protein.[11] Ivacaftor is an approved CFTR potentiator that increases the open probability of CFTR channels (i.e., the fraction of time that the channels are open) in vitro and improves clinical outcomes in patients 6 years of age or older who have cystic fibrosis and at least one copy of most class III (gating) mutations.[12-17] In vitro studies have shown that ivacaftor also potentiates surface-localized p.Phe508del CFTR,[18] and the combination of lumacaftor with ivacaftor has been associated with a greater increase in chloride transport than has either agent alone.[11]

Although neither ivacaftor nor lumacaftor monotherapy has been shown to have meaningful clinical efficacy in patients who are homozygous for the Phe508del *CFTR* mutation,[19,20] a phase 2 study suggested that the combination of lumacaftor and ivacaftor increased CFTR activity to a degree that may be sufficient to improve clinical outcomes in these patients.[21] Therefore, two phase 3 trials (TRAFFIC and TRANSPORT) were conducted to evaluate the efficacy and safety of two different doses of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the Phe508del *CFTR* mutation.

METHODS

STUDY DESIGN AND OVERSIGHT

The TRAFFIC and TRANSPORT trials were two phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group studies in which lumacaftor (VX-809, Vertex Pharmaceuticals) was orally administered in combination with ivacaftor (VX-770, Vertex Pharmaceuticals) for 24 weeks; the studies were conducted from April 2013 through April 2014. The study design and methods of data analysis were identical for the two studies, with the exception of the inclusion of ambulatory electrocardiography (TRAFFIC only) and adolescent pharmacokinetic assessments (TRANSPORT only) for a subgroup of patients. The studies were designed to evaluate the efficacy of lumacaftor–ivacaftor in patients with cystic fibrosis who were homozygous for the Phe508del *CFTR* mutation; the evaluation of safety was a secondary objective. The protocols (available with the full text of this article at NEJM.org) were reviewed and approved by an ethics committee at each of the 187 participating centers; all patients provided written informed consent.

Patients were randomly assigned (in a 1:1:1 ratio) to one of three study groups (Fig. S1 in the Supplementary Appendix, available at NEJM.org): 600 mg of lumacaftor once daily in combination with 250 mg of ivacaftor every 12 hours (LUM [600 mg/day]–IVA), 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours (LUM [400 mg every 12 hr]–IVA), or lumacaftor-matched placebo every 12 hours in combination with ivacaftor-matched placebo every 12 hours. All regimens were given for 24 weeks. Randomization was stratified according to age (<18 years vs. ≥18 years), sex, and pulmonary function (percentage of predicted forced expiratory volume in 1 second [FEV_1] at screening, <70 vs. ≥70).

The sponsor of the studies (Vertex Pharmaceuticals) designed the protocol in collaboration with the authors. Site investigators collected the data, which were analyzed by the sponsor. All the authors had full access to the study data after the study periods were complete and the data were unblinded. The authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocols, which are available at NEJM.org.

STUDY PARTICIPANTS

Eligibility criteria included a confirmed diagnosis of cystic fibrosis, homozygosity for the Phe508del *CFTR* mutation, an age of 12 years or older, a percentage of predicted FEV_1 at the time of screening that was 40 to 90% of the predicted normal values,[22,23] and stable cystic fibrosis disease. Between the screening and baseline visits (≤4 weeks), fluctuation in FEV_1 occurred in some cases and was documented; 81 patients had an FEV_1 that fell to below 40% of the predicted value at baseline. Patients continued to take their prestudy medications.

STUDY ASSESSMENTS

All assessments were prespecified in the study protocols and statistical analysis plans unless otherwise noted. The primary end point was the absolute change from baseline at week 24 in the percentage of predicted FEV_1, calculated by averaging the mean absolute change at week 16 and the mean absolute change at week 24; this approach was used because we anticipated that it would reduce variability, as compared with using the point estimate at week 24 alone. Key secondary end points included the relative change from baseline in the percentage of predicted FEV_1 (calculated by averaging the mean values for weeks 16 and 24), the absolute change from baseline at week 24 in body-mass index (BMI), the absolute change from baseline at week 24 in the patient-reported Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score (scores range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status),[24] the percentage of patients with a relative increase from baseline of 5% or higher in the percentage of predicted FEV_1 (calculated by averaging the mean values for weeks 16 and 24), and the number of pulmonary exacerbations through week 24. The time to the first pulmonary exacerbation was assessed, as was the absolute change in body weight. The safety of the study regimens was also evaluated. Subgroup analyses and additional assessments of exacerbation, including assessments of the numbers of patients requiring hospitalization and those requiring treatment with intravenous antibiotics, were also performed.

STATISTICAL ANALYSES

All patients who underwent randomization and received at least one dose of study drug were included in the efficacy analysis, in which patients were analyzed as part of the study group to which they were randomly assigned (full analysis set). In the primary analysis, we evaluated the treatment difference in the percentage of predicted FEV_1 at week 24, which was assessed as the difference between the treatment groups and the placebo group in the primary end point.

The safety set included all patients who received any amount of study drug; data were analyzed according to the patients' actual study group (regardless of the group to which they had been randomly assigned). The reported adverse events are those that either developed or increased in severity at or after the time patients received the initial dose of study drug, up to 28 days after receipt of the last dose. Additional details regarding the statistical analysis, including the hierarchical testing procedure for the multiple end points and the criteria for the assessment of statistical significance, are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

Of the 1122 patients who underwent randomization (559 in the TRAFFIC study and 563 in the TRANSPORT study), 1108 received at least one dose of study drug or placebo (Fig. S2 in the Supplementary Appendix). The baseline demographic and other characteristics were well balanced across study groups (Table 1, and Table S1 in the Supplementary Appendix). The mean baseline FEV_1 was 61% of the predicted value. At baseline, a high percentage of patients reported maintenance use of multiple pulmonary, nutritional, and other cystic fibrosis therapies. The majority of patients completed their assigned study regimens: 348 patients in the LUM (600

Table 1. Baseline Characteristics and Demographic Data.*

Characteristic	Placebo (N=371)	LUM (600 mg/day)–IVA (N=368)	LUM (400 mg every 12 hr)–IVA (N=369)
Female sex — no. (%)	181 (48.8)	182 (49.5)	182 (49.3)
Mean age (range) — yr	25.4 (12–64)	24.5 (12–54)	25.3 (12–57)
Age group — no. (%)			
12 to <18 yr	96 (25.9)	96 (26.1)	98 (26.6)
≥18 yr	275 (74.1)	272 (73.9)	271 (73.4)
Percentage of predicted FEV_1 at baseline			
Mean (range)	60.4 (33.9–99.8)	60.8 (31.1–92.3)	60.5 (31.3–96.5)
Subgroup — no. (%)			
<40	28 (7.5)	24 (6.5)	29 (7.9)
≥40 to <70	238 (64.2)	241 (65.5)	233 (63.1)
≥70 to ≤90	97 (26.1)	98 (26.6)	100 (27.1)
>90	3 (0.8)	3 (0.8)	3 (0.8)
Mean BMI (range)†	21.0 (14.1–32.2)	21.0 (14.2–35.1)	21.5 (14.6–31.4)
Maintenance use of pulmonary or respiratory cystic fibrosis therapy at baseline — no. (%)			
Bronchodilators	342 (92.2)	342 (92.9)	344 (93.2)
Dornase alfa	281 (75.7)	289 (78.5)	273 (74.0)
Inhaled antibiotics	258 (69.5)	232 (63.0)	225 (61.0)
Azithromycin	233 (62.8)	233 (63.3)	215 (58.3)
Inhaled hypertonic saline	220 (59.3)	197 (53.5)	227 (61.5)
Inhaled glucocorticoids	220 (59.3)	213 (57.9)	212 (57.5)

* The LUM (600 mg/day)–IVA group received 600 mg of lumacaftor (LUM) once daily in combination with 250 mg of ivacaftor (IVA) every 12 hours; the LUM (400 mg every 12 hr)–IVA group received 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours. FEV_1 denotes forced expiratory volume in 1 second.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

mg/day)–IVA group (94.6%), 344 patients in the LUM (400 mg every 12 hr)–IVA group (93.2%), and 362 patients in the placebo group (97.6%).

CLINICAL EFFICACY

In both studies, FEV_1 improvements were observed as early as day 15 and were sustained through 24 weeks in both lumacaftor–ivacaftor dose groups (Fig. 1A, and Fig. S3 and S4 in the Supplementary Appendix). The difference between lumacaftor–ivacaftor and placebo with respect to the mean absolute change in the percentage of predicted FEV_1 from baseline at week 24 was significant in all dose groups and ranged from 2.6 to 4.0 percentage points ($P<0.001$ for all comparisons) (Table 2). The difference between lumacaftor–ivacaftor and placebo with respect to the mean relative change in FEV_1 was also significant and ranged from 4.3 to 6.7% ($P<0.001$ for all groups) (Table 2). In each study, the percentage of patients who had a relative improvement in the percentage of predicted FEV_1 of 5% or higher was greater in the lumacaftor–ivacaftor groups than in the placebo group ($P<0.001$ to $P=0.002$ for the odds ratio) but was not significant in the testing hierarchy (Table 2, and Table S2 in the Supplementary Appendix). In the pooled analysis, approximately twice as many patients in the lumacaftor–ivacaftor groups as in the placebo group had a relative improvement in the percentage of predicted FEV_1 of 5% or higher (39 to 46% vs. 22%) and 10% or higher (24 to 27% vs. 13%) (Table 2, and Table S2 and Fig. S5 in the Supplementary Appendix). The mean absolute change in the percentage of predicted FEV_1 was also assessed in a variety of subgroups (e.g., subgroups defined according to various baseline characteristics and concomitant

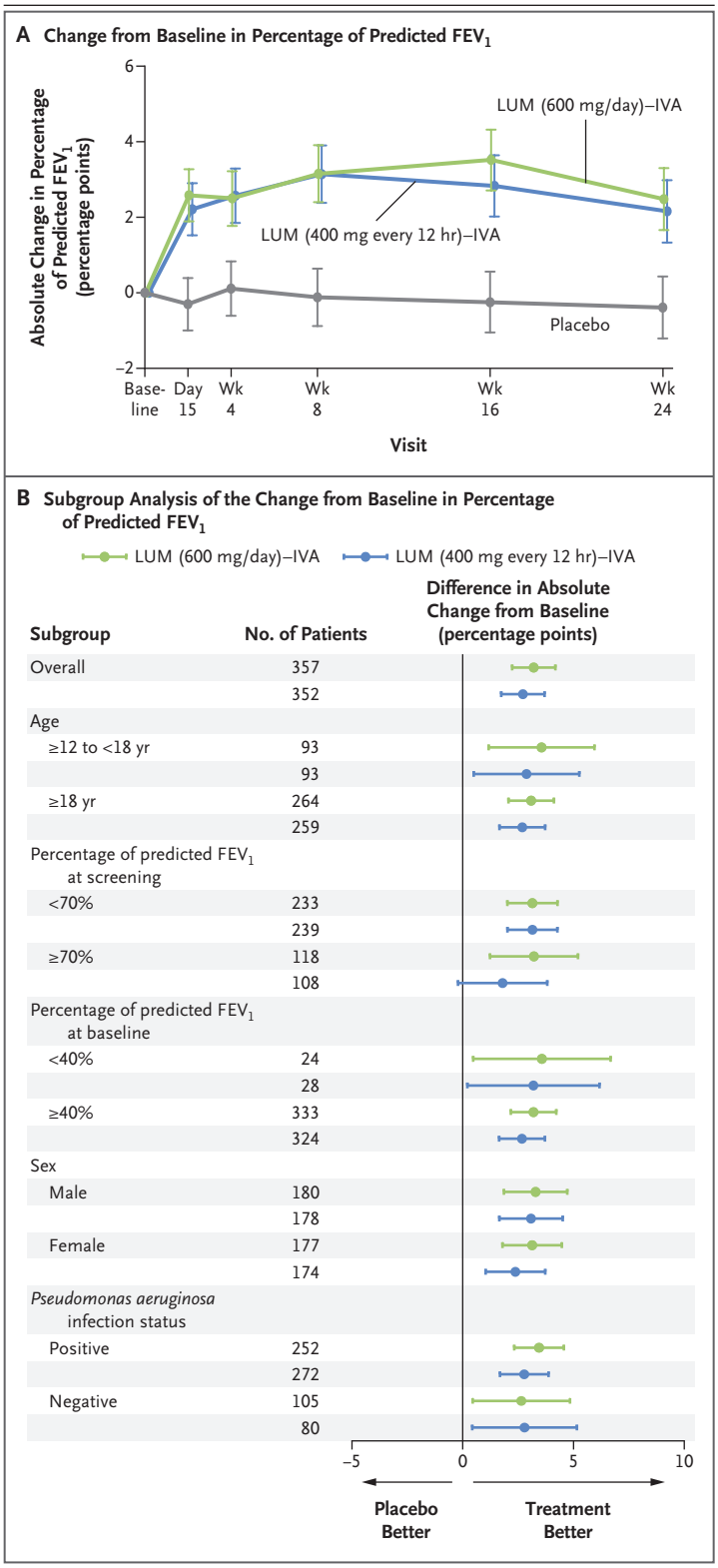

Figure 1. Absolute Changes from Baseline in the Percentage of Predicted Forced Expiratory Volume in 1 Second (FEV_1) According to Study Group.

The LUM (600 mg/day)–IVA group received 600 mg of lumacaftor (LUM) once daily in combination with 250 mg of ivacaftor (IVA) every 12 hours; the LUM (400 mg every 12 hr)–IVA group received 400 mg of lumacaftor every 12 hours in combination with 250 mg of ivacaftor every 12 hours. Panel A shows the mean absolute change in the percentage of predicted FEV_1 over time in each study group; the difference between each active-treatment group and the placebo group at each time point was significant ($P<0.025$). Panel B shows subgroup analyses of the differences between the active treatment and placebo in the absolute change from baseline in the percentage of predicted FEV_1 at week 24. Data in both panels are least-squares means; I bars indicate 95% confidence intervals. The results represent pooled data from the TRAFFIC and TRANSPORT studies.

medications); the improvement in the percentage of predicted FEV_1 in the lumacaftor–ivacaftor groups versus the placebo group was consistent across all subgroups (Fig. 1B, and Fig. S6 in the Supplementary Appendix). Additional details are provided in the Supplementary Appendix.

Clinically meaningful reductions in the rates of protocol-defined pulmonary exacerbations were seen in both lumacaftor–ivacaftor dose groups. The rate ratio (lumacaftor–ivacaftor vs. placebo) ranged from 0.57 to 0.72 ($P<0.001$ to $P=0.05$; none of the rate ratios were considered significant in the testing hierarchy) (Table 2, and Table S2 in the Supplementary Appendix). In the pooled analysis, the rate of exacerbations was significantly lower in both lumacaftor–ivacaftor dose groups than in the placebo group: 30% lower in the LUM (600 mg/day)–IVA group and 39% lower in the LUM (400 mg every 12 hr)–IVA group ($P=0.001$ and $P<0.001$, respectively) (Table 2, and Table S2 in the Supplementary Appendix). Through week 24, the proportion of patients who remained free from exacerbations in the pooled analysis was significantly higher in both lumacaftor–ivacaftor groups than in the placebo group, and the risk of having an exacerbation was significantly lower in the lumacaftor–ivacaftor groups (Fig. 2A and Table 2). Additional analyses revealed significant reductions with lumacaftor–ivacaftor therapy in the number of exacerbations leading to hospitalizations and those necessitating the administration of intravenous antibiotics (Fig. 2B).

Over the course of the 24-week period, the mean BMI (the weight in kilograms divided by the square of the height in meters) increased steadily in both lumacaftor–ivacaftor dose groups (Fig. S7 in the Supplementary Appendix).

In the analysis of the individual trials, the difference between lumacaftor–ivacaftor and placebo with respect to the absolute change in BMI was significant for both dose groups in the TRANSPORT study but for neither dose group in the TRAFFIC study (Table 2). In the pooled analysis at week 24, the treatment difference versus placebo with respect to the absolute change in BMI was 0.24 to 0.28 (P<0.001) (Table 2, and Table S2 and Fig. S7 in the Supplementary Appendix); this represents an improvement of approximately 1% with lumacaftor–ivacaftor. Across the lumacaftor–ivacaftor dose groups in TRAFFIC and TRANSPORT, the least-squares mean change from baseline in body weight at week 24 ranged from 1.23 to 1.57 kg.

The CFQ-R is a cystic fibrosis–specific instrument that is designed to evaluate patient-reported assessments of various health-related measures. In both lumacaftor–ivacaftor dose groups, there were improvements in the within-group CFQ-R respiratory domain score; the treatment difference versus placebo was nominally significant (on the basis of the testing hierarchy) in the analysis of the individual trials only for the LUM (600 mg/day)–IVA group in the TRAFFIC study; the treatment difference reached significance in the LUM (600 mg/day)–IVA group in the pooled analysis (Table 2, and Fig. S8 in the Supplementary Appendix).

SAFETY

Overall, the proportion of patients reporting adverse events was similar across the lumacaftor–ivacaftor groups and the placebo group (Table 3). Pooled across the studies, serious adverse events were reported in 28.6% of the patients in the placebo group and in 17.3 to 22.8% of the patients in the lumacaftor–ivacaftor groups. In all the groups, infective pulmonary exacerbation was the most common serious adverse event (occurring in 24.1% of the patients in the placebo group and in 13.0% of those in the pooled lumacaftor–ivacaftor groups). The proportion of patients who discontinued the study regimen because of an adverse event was higher in the lumacaftor–ivacaftor groups than in the placebo group (4.2% [31 of 738 patients] vs. 1.6% [6 of 370 patients]). Among the patients receiving lumacaftor–ivacaftor, the adverse events that led to discontinuation of the study regimen in two or more patients were elevation of the creatine kinase level (4 patients), hemoptysis (3), bronchospasm (2), dyspnea (2), pulmonary exacerbation (2), and rash (2). No deaths were reported.

The adverse events reported more frequently in the lumacaftor–ivacaftor groups were generally respiratory in nature. The majority were of mild-to-moderate severity and included dyspnea and chest tightness (Table 3, and Table S3 in the Supplementary Appendix). Two patients in the placebo group (one with dyspnea and one with chest discomfort) and four patients in the LUM (600 mg/day)–IVA group (two with dyspnea and two with bronchospasm) had adverse events of respiratory symptoms or reactive airways that were severe. In patients who had respiratory-symptom adverse events within 1 to 2 days after the initiation of therapy and who did not discontinue the study regimen, the events generally resolved within the first 2 to 3 weeks of therapy. Beyond the first week of therapy, the incidence of respiratory events was similar in the lumacaftor–ivacaftor and placebo groups. In addition, the pattern of adverse events according to the severity of lung disease at baseline was generally similar across the groups.

Elevations in levels of alanine or aspartate aminotransferase to more than 3 times the upper limit of the normal range were observed in 5.1% of the patients in the placebo group and in 5.2% of those in the lumacaftor–ivacaftor groups (Table S4 in the Supplementary Appendix). Serious adverse events related to abnormal liver function were not observed in the placebo group and were reported for seven patients in the lumacaftor–ivacaftor groups. After discontinuation or interruption of lumacaftor–ivacaftor therapy, liver function in all patients improved substantially, and results of liver-function tests returned to baseline in the case of six patients. Details regarding these events, including concomitant elevations in bilirubin, are provided in the Supplementary Appendix.

DISCUSSION

Significant improvements in the percentage of predicted FEV_1 were seen in all four lumacaftor–ivacaftor treatment groups in the TRAFFIC and TRANSPORT studies. In both dose groups in each study, improvements in FEV_1 were seen by day 15 and were sustained throughout the 24-week study period.

Lumacaftor–ivacaftor combination therapy

Table 2. Efficacy Results at Week 24.*

Result	TRAFFIC			TRANSPORT			Pooled		
	Placebo (N=184)	LUM (600 mg/day)–IVA (N=183)	LUM (400 mg every 12 hr)–IVA (N=182)	Placebo (N=187)	LUM (600 mg/day)–IVA (N=185)	LUM (400 mg every 12 hr)–IVA (N=187)	Placebo (N=371)	LUM (600 mg/day)–IVA (N=368)	LUM (400 mg every 12 hr)–IVA (N=369)
Change in percentage of predicted FEV_1 from baseline†									
Difference vs. placebo in the absolute change — percentage points									
Mean (95% CI)	—	4.0 (2.6 to 5.4)‡	2.6 (1.2 to 4.0)‡	—	2.6 (1.2 to 4.1)‡	3.0 (1.6 to 4.4)‡	—	3.3 (2.3 to 4.3)‡	2.8 (1.8 to 3.8)‡
P value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Difference vs. placebo in the relative change — %									
Mean (95% CI)	—	6.7 (4.3 to 9.2)‡	4.3 (1.9 to 6.8)‡	—	4.4 (1.9 to 7.0)‡	5.3 (2.7 to 7.8)‡	—	5.6 (3.8 to 7.3)‡	4.8 (3.0 to 6.6)‡
P value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Difference vs. placebo in absolute change from baseline in BMI									
Mean (95% CI)	—	0.16 (–0.04 to 0.35)	0.13 (–0.07 to 0.32)	—	0.41 (0.23 to 0.59)‡	0.36 (0.17 to 0.54)‡	—	0.28 (0.15 to 0.41)‡	0.24 (0.11 to 0.37)‡
P value		0.11	0.19		<0.001	<0.001		<0.001	<0.001
Difference vs. placebo in absolute change from baseline in CFQ-R respiratory domain									
Mean (95% CI) — points	—	3.9 (0.7 to 7.1)	1.5 (–1.7 to 4.7)	—	2.2 (–0.9 to 5.3)	2.9 (–0.3 to 6.0)	—	3.1 (0.8 to 5.3)‡	2.2 (0.0 to 4.5)
P value		0.02	0.36		0.17	0.07		0.007	0.05
Odds ratio for a relative increase of ≥5% from baseline in the percentage of predicted FEV_1									
Odds ratio (95% CI)	—	2.9 (1.9 to 4.6)	2.1 (1.3 to 3.3)	—	3.0 (1.9 to 4.6)	2.4 (1.5 to 3.7)	—	2.9 (2.1 to 4.0)‡	2.2 (1.6 to 3.1)‡
P value		<0.001	0.002		<0.001	<0.001		<0.001	<0.001
Pulmonary exacerbations§									
Events — no. (rate per 48 wk)	112 (1.07)	79 (0.77)	73 (0.71)	139 (1.18)	94 (0.82)	79 (0.67)	251 (1.14)	173 (0.80)	152 (0.70)

Result	TRAFFIC			TRANSPORT			Pooled		
	Placebo (N=184)	LUM (600 mg/day)–IVA (N=183)	LUM (400 mg every 12 hr)–IVA (N=182)	Placebo (N=187)	LUM (600 mg/day)–IVA (N=185)	LUM (400 mg every 12 hr)–IVA (N=187)	Placebo (N=371)	LUM (600 mg/day)–IVA (N=368)	LUM (400 mg every 12 hr)–IVA (N=369)
Rate ratio (95% CI)	—	0.72 (0.52 to 1.00)	0.66 (0.47 to 0.93)	—	0.69 (0.52 to 0.92)	0.57 (0.42 to 0.76)	—	0.70 (0.56 to 0.87)‡	0.61 (0.49 to 0.76)‡
P value for the rate ratio		0.05	0.02		0.01	<0.001		0.001	<0.001

* Reported means are least-squares means. For individual studies, within each active-treatment group and between the active-treatment groups and the placebo group, a hierarchical testing procedure was performed to control for multiplicity across primary and key secondary end points; P≤0.0250 in the current test and all previous tests was required to claim significance in the hierarchy. CFQ-R denotes Cystic Fibrosis Questionnaire–Revised.
† Changes in the percentage of predicted FEV_1 are calculated by averaging the means at weeks 16 and 24.
‡ The difference versus placebo was significant.
§ The number of pulmonary exacerbations was reported through week 24 and is expressed as a rate over 48 weeks.

resulted in improvements in multiple clinical end points, and the findings were generally consistent across dose groups and studies. Clinically important reductions in the rate of pulmonary exacerbations were also observed in association with lumacaftor–ivacaftor therapy. Through 24 weeks, the lumacaftor–ivacaftor groups had reductions in the rate of pulmonary exacerbations, with decreases in the numbers of events leading to hospitalization or intravenous antibiotic treatment. FEV_1 and rates of pulmonary exacerbations are strong predictors of survival and thus remain important for the evaluation of new therapies for cystic fibrosis.[25]

Significant improvements (i.e., increases) in BMI were observed in the TRANSPORT study and in the pooled analyses but not in the TRAFFIC study. Across both studies, BMI continued to increase during the study period in both lumacaftor–ivacaftor groups. Although the mechanisms for improvement in the nutritional status of patients with cystic fibrosis are not fully defined, the gains are hypothesized to reflect either better caloric absorption, possibly due to normalized intestinal pH,[17] or a reduction in energy expenditure resulting from amelioration of lung disease.[17,26] Numerical increases in the CFQ-R respiratory domain score favoring active treatment were seen in both dose groups in both studies; however, in the pooled analysis of that score, the treatment difference was significant only in the LUM (600 mg/day)–IVA group and did not meet the requirement for a minimum clinically important difference (4 points).[24] It is challenging to interpret these results, given the significant improvements in FEV_1. The CFQ-R instrument is valuable for assessing patient-reported outcomes; however, there is precedent for a lack of correlation with FEV_1. Studies of tobramycin showed no correlation between changes in CFQ-R and FEV_1.[24] It is also worth noting that the CFQ-R minimum clinically important difference was established as a within-group change in patients who had markers of advanced disease, which complicates its application to other populations.[24]

The TRAFFIC and TRANSPORT study cohorts were a population with well-managed cystic fibrosis, as evidenced by the minimal FEV_1 deterioration in the placebo group and the high rates of the use of standard cystic fibrosis therapy. The magnitude of the change in FEV_1 was sig-

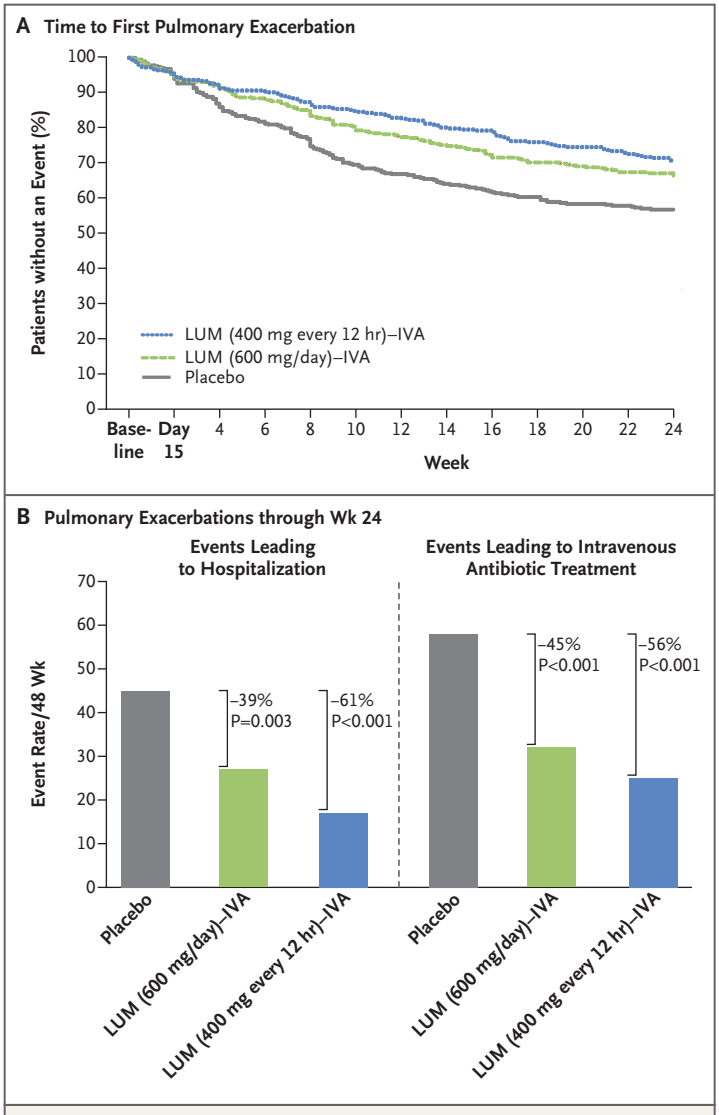

Figure 2. Pulmonary Exacerbations.

The time to first pulmonary exacerbation and number of pulmonary exacerbations leading to hospitalization or treatment with intravenous antibiotics are shown. In Panel B, the number of pulmonary exacerbations observed through week 24 is expressed as a rate over 48 weeks. The results represent pooled data from the TRAFFIC and TRANSPORT studies.

nificant and was in the range of the magnitudes of change seen in studies of other cystic fibrosis therapeutics.[27-31] The changes due to treatment in the percentage of predicted FEV_1 were largely consistent across studies, dose groups, and all subgroups analyzed, including subgroups defined according to age, baseline FEV_1 (<40 vs. ≥40), and status with respect to *Pseudomonas aeruginosa* infection. Improvements in FEV_1 and BMI and reductions in exacerbations were observed while patients continued to use their prescribed cystic fibrosis therapies; lumacaftor–ivacaftor is therefore expected to provide a clinically meaningful benefit in addition to the standard of care. The determination of the potential for lumacaftor–ivacaftor–mediated CFTR modulation to modify the course of disease will require additional analyses and longer-term data.

Although the improvements in FEV_1 associated with lumacaftor–ivacaftor were significant and consistent with in vitro[11] and phase 2 sweat chloride and FEV_1 results,[21] the effect of lumacaftor–ivacaftor on sweat chloride and FEV_1 was smaller than that observed in patients with the Gly551Asp mutation who were treated with ivacaftor monotherapy.[13,14] Whereas CFTR with the p.Gly551Asp mutation has a gating defect but is found at the cell surface, CFTR with the p.Phe508del mutation has multiple defects, which makes addressing the underlying cause of disease in patients homozygous for this mutation more complex. The most important of these defects is a substantial reduction in processing and transport to the cell surface, plus a reduced stability and channel gating of the few surface-localized proteins. These multiple defects make restoring p.Phe508del CFTR activity and subsequent observation of a clinical benefit more challenging than addressing the p.Gly551Asp gating defect. The smaller changes in sweat chloride and FEV_1 seen in association with lumacaftor–ivacaftor therapy in patients homozygous for Phe508del, as compared with the changes seen in association with ivacaftor monotherapy in patients with Gly551Asp, was predicted in vitro and may be due in part to the fact that lumacaftor only partially rescues the p.Phe508del CFTR processing defect,[11] which results in fewer p.Phe508del CFTR channels at the cell surface than are seen with p.Gly551Asp CFTR.

Two in vitro studies have suggested that treatment (for ≤48 hours) with potentiators, including ivacaftor, may reduce the stability and expression of corrected p.Phe508del.[32,33] Although it is possible that ivacaftor affects the steady-state levels of corrected p.Phe508del CFTR in vitro, the results of the TRAFFIC and TRANSPORT studies, which included more than 1100 patients, suggest that lumacaftor–ivacaftor provides a clinical benefit that is greater than that previously observed with either agent alone.[20,21] Moreover, the clinical benefit was sustained for the entire duration of the studies.

Table 3. Adverse Events Associated with the Study Regimens.*

Event	Placebo (N=370)	LUM (600 mg/day)–IVA (N=369)	LUM (400 mg every 12 hr)–IVA (N=369)
		number of patients (percent)	
Any adverse event reported	355 (95.9)	356 (96.5)	351 (95.1)
Discontinuation of the study regimen because of an adverse event	6 (1.6)	14 (3.8)	17 (4.6)
At least one serious adverse event	106 (28.6)	84 (22.8)	64 (17.3)
Most common adverse events†			
Infective pulmonary exacerbation of cystic fibrosis	182 (49.2)	145 (39.3)	132 (35.8)
Cough	148 (40.0)	121 (32.8)	104 (28.2)
Headache	58 (15.7)	58 (15.7)	58 (15.7)
Increase in sputum production	70 (18.9)	55 (14.9)	54 (14.6)
Dyspnea	29 (7.8)	55 (14.9)	48 (13.0)
Hemoptysis	50 (13.5)	52 (14.1)	50 (13.6)
Diarrhea	31 (8.4)	36 (9.8)	45 (12.2)
Nausea	28 (7.6)	29 (7.9)	46 (12.5)
Abnormal respiration (chest tightness)	22 (5.9)	40 (10.8)	32 (8.7)
Nasopharyngitis	40 (10.8)	23 (6.2)	48 (13.0)
Oropharyngeal pain	30 (8.1)	44 (11.9)	24 (6.5)
Upper respiratory tract infection	20 (5.4)	24 (6.5)	37 (10.0)
Nasal congestion	44 (11.9)	33 (8.9)	24 (6.5)
Serious adverse events occurring in at least 3 patients in any treatment group			
Infective pulmonary exacerbation of cystic fibrosis	89 (24.1)	55 (14.9)	41 (11.1)
Hemoptysis	3 (0.8)	4 (1.1)	5 (1.4)
Distal intestinal obstruction syndrome	5 (1.4)	2 (0.5)	2 (0.5)

* The reported adverse events are those that either developed or increased in severity at or after the time patients received the initial dose of study drug (placebo or active agent), up to 28 days after receipt of the last dose.

† The most common adverse events were defined as those that occurred in at least 10% of patients in any treatment group.

Nevertheless, the differences between the results of treatment with lumacaftor–ivacaftor in patients with the Phe508del mutation and treatment with ivacaftor in patients with the Gly551Asp mutation point to the need for continued development of CFTR modulators that will further improve on the meaningful FEV_1 benefits observed in the TRAFFIC and TRANSPORT studies.

Lumacaftor–ivacaftor therapy at both dosing regimens generally had an acceptable side-effect profile. The proportion of patients who discontinued the study regimen for reasons related to an adverse event was higher among those who received lumacaftor–ivacaftor than among those who received placebo, and dyspnea and chest tightness were reported more frequently in the active-treatment groups. In a phase 2 study, treatment with lumacaftor monotherapy was associated with an initial increased risk of dyspnea or chest tightness, although these symptoms were uncommon after the addition of ivacaftor to lumacaftor.[21] Elevated levels of liver enzymes were observed in a similar number of patients in the active-treatment groups and the placebo group; however, serious adverse events related to elevation of liver enzymes were reported only in the active-treatment group.

The TRAFFIC and TRANSPORT studies included the same two doses of lumacaftor so that we could ascertain whether there was a dose response for the CFTR corrector. Pooled across the two

studies, the dose regimens appeared to have similar efficacy and safety profiles, with no clear differentiation except with respect to pulmonary exacerbation–related outcomes, which consistently favored the LUM (400 mg every 12 hr)–IVA group.

In conclusion, in the TRAFFIC and TRANSPORT studies, lumacaftor in combination with ivacaftor improved FEV_1 and reduced the rate of pulmonary exacerbations in patients with cystic fibrosis who were homozygous for the Phe508del *CFTR* mutation. Lumacaftor–ivacaftor therapy generally had an acceptable side-effect profile, with more than 93% of patients completing the assigned therapy regimen. These data show that the combination of a CFTR corrector and potentiator, designed to address the underlying cause of cystic fibrosis by targeting CFTR, can benefit patients who are homozygous for the Phe508del *CFTR* mutation and represents a treatment milestone for the 45% of patients with cystic fibrosis who are homozygous for this mutation.

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APPENDIX

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