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Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del *CFTR* by pulmonary function subgroup

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Research in context

Evidence before this study

We searched PubMed on April 12, 2016 for the terms “ivacaftor” or “VX-770”, “lumacaftor” or “VX-809”, and “clinical trial” with no restrictions on publication date or language and retrieved three relevant clinical studies. In Phase 2 studies, combination lumacaftor/ivacaftor therapy, but not monotherapy, improved lung function and had an acceptable side-effect profile in patients with cystic fibrosis (CF) homozygous for the Phe508del *CFTR* mutation. The Phase 3 TRAFFIC and TRANSPORT studies demonstrated a clinically meaningful benefit of lumacaftor/ivacaftor combination therapy in this population. To be eligible for these studies patients had to have a screening percent predicted forced expiratory volume 1 second ($ppFEV_1$) of 40 to 90. Therefore, few data are available on which to base treatment decisions in patients whose $ppFEV_1$ is below 40.

Added value of this study

We evaluated the response to lumacaftor/ivacaftor therapy in the Phase 3 TRAFFIC and TRANSPORT studies among patients with CF homozygous for the Phe508del *CFTR* mutation stratified by specific categories of lung function, including a subgroup of patients with severe lung dysfunction whose $ppFEV_1$ declined to below 40 percentage points between screening and baseline. This provided an opportunity to assess the response in this group of patients that is often not studied. Results of this prespecified subgroup analysis provide evidence that lumacaftor/ivacaftor therapy improved $ppFEV_1$

levels in patients across a spectrum of pretreatment lung function. The incidence of some respiratory adverse events (AEs) was higher among patients with baseline ppFEV$_1$ <40 than those with baseline ppFEV$_1$ ≥40. Across lung function subgroups, some respiratory AEs occurred more frequently in patients who received lumacaftor/ivacaftor therapy than placebo. These respiratory AEs were associated with the initiation of treatment, irrespective of lung function subgroup, and usually resolved with continued treatment. Discontinuations due to AEs were low and similar across subgroups.

Implications of all the available evidence

These data demonstrate that lumacaftor/ivacaftor combination therapy benefits patients with CF homozygous for the Phe508del *CFTR* mutation with varying degrees of lung function impairment, including those with moderate to severe dysfunction. Prospective evaluation is warranted in patients with ppFEV$_1$ values below 40, in particular among those with ppFEV$_1$ values below 30, in whom the safety and efficacy of lumacaftor/ivacaftor combination therapy are currently being evaluated.

Summary

Background Lumacaftor/ivacaftor combination therapy demonstrated clinical benefits in patients with cystic fibrosis homozygous for the Phe508del *CFTR* mutation. Pretreatment lung function is a confounding factor that potentially impacts the efficacy and safety of lumacaftor/ivacaftor therapy.

Methods Two multinational, randomised, double-blind, placebo-controlled, parallel-group Phase 3 studies randomised patients to receive placebo or lumacaftor (600 mg once daily [qd] or 400 mg every 12 hours [q12h]) in combination with ivacaftor (250 mg q12h) for 24 weeks. Prespecified analyses of pooled efficacy and safety data by lung function, as measured by percent predicted forced expiratory volume in 1 second ($ppFEV_1$), were performed for patients with baseline $ppFEV_1$ <40 (n=81) and ≥40 (n=1016) and screening $ppFEV_1$ <70 (n=730) and ≥70 (n=342). These studies were registered with ClinicalTrials.gov (NCT01807923 and NCT01807949).

Findings The studies were conducted from April 2013 through April 2014. Improvements in the primary endpoint, absolute change from baseline at week 24 in $ppFEV_1$, were observed with both lumacaftor/ivacaftor doses in the subgroup with baseline $ppFEV_1$ <40 (least-squares mean difference versus placebo was 3·7 and 3.3 percentage points for lumacaftor 600 mg qd/ivacaftor 250 mg q12h and lumacaftor 400 mg q12h/ivacaftor 250 mg q12h, respectively [p<0·05] and in the subgroup with baseline $ppFEV_1$ ≥40 (3·3 and 2·8 percentage points, respectively [p<0·001]). Similar absolute improvements versus placebo in $ppFEV_1$ were observed in subgroups with screening

ppFEV$_1$ <70 (3·3 and 3·3 percentage points for lumacaftor 600 mg qd/ivacaftor 250 mg q12h and lumacaftor 400 mg q12h/ivacaftor 250 mg q12h, respectively [p<0·001]) and ≥70 (3·3 and 1·9 percentage points, respectively [p=0.002] and [p=0·079]). Increases in BMI and reduction in number of pulmonary exacerbation events were observed in both LUM/IVA dose groups vs placebo across all lung function subgroups. Treatment was generally well tolerated, although the incidence of some respiratory adverse events was higher with active treatment than with placebo.

Interpretation Lumacaftor/ivacaftor combination therapy benefits patients homozygous for Phe508del *CFTR* who have varying degrees of lung function impairment.

Funding Vertex Pharmaceuticals Incorporated.

Introduction

The most common cystic fibrosis (CF)-causing mutation, Phe508del CF transmembrane conductance regulator (*CFTR)*, leads to a variety of defects, including reduced folding and trafficking of the CFTR protein to the epithelial cell surface and defective channel gating, among others.[1–4] Therefore, restoring the chloride transport activity of the Phe508del CFTR channel is complex. Lumacaftor (LUM) is a CFTR corrector, which selectively increases the processing and trafficking of Phe508del *CFTR* to the cell surface and enhances CFTR–mediated chloride transport in vitro.[5] Ivacaftor (IVA) is a CFTR potentiator, which facilitates chloride transport by increasing the channel-open probability of CFTR on the cell surface.[6] Monotherapy with either LUM or IVA was not shown to be clinically beneficial in patients with CF homozygous for the Phe508del *CFTR* mutation.[7,8] In contrast, clinically meaningful benefits were observed with combination therapy in patients with CF homozygous for the Phe508del *CFTR* mutation in a Phase 2[9] and in two Phase 3, randomised, double-blind, placebo-controlled studies, TRAFFIC and TRANSPORT.[10]

Significant improvements in lung function were observed with LUM 600 mg once daily (qd)/IVA 250 mg every 12 hours (q12h) and LUM 400 mg q12h/IVA 250 mg q12h in the TRAFFIC and TRANSPORT studies; the mean absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at week 24 versus placebo ranged from 2·8 to 3·3 percentage points in the pooled analysis ($p<0·001$).[10] Improvements were also observed in nutritional status and rate of pulmonary exacerbations (PEx). These data supported the approval of LUM/IVA combination therapy (Orkambi; Vertex

Pharmaceuticals Incorporated; Boston, MA, USA) in patients aged 12 and older with CF homozygous for the Phe508del *CFTR* mutation in the United States, the European Union, and Canada.

Patients with CF whose $ppFEV_1$ is in the severe range have a greater burden of disease associated with a higher rate of PEx and worse nutritional status.[11,12] The safety and efficacy of new treatments in patients with severe lung dysfunction may not be the same as in patients with milder dysfunction. The TRAFFIC and TRANSPORT studies enrolled patients with $ppFEV_1$ values of 40 to 90 percentage points at screening, reflecting a range of lung function impairment from mild ($ppFEV_1$ ≥70 to ≤90) to moderate ($ppFEV_1$ 40 to 69). Some patients had a $ppFEV_1$ value that decreased to below 40 between screening and baseline, providing an opportunity to assess treatment response in this clinically important subgroup.[10] Prospective evaluation of the safety and efficacy of LUM/IVA in patients with severe lung dysfunction is ongoing. Here, we describe a prespecified pooled analysis of data from the TRAFFIC and TRANSPORT studies performed to determine the efficacy and safety of LUM/IVA combination therapy in patients with CF homozygous for the Phe508del *CFTR* mutation, defined by specific categories of lung function, including those with severe lung dysfunction ($ppFEV_1$ <40 at baseline).

Methods

Study design and patients

The TRAFFIC and TRANSPORT trials were multinational, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 studies conducted from April 2013 through April 2014. Both studies were conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines and all applicable local and national regulations. The study protocol was approved by ethics committees, and all patients provided written informed consent.

The design of these nearly identical studies has been described previously and is briefly reviewed in the supplemental appendix.[10] The studies included patients aged 12 years or older with a confirmed diagnosis of CF, homozygous for the Phe508del *CFTR* mutation, and a $ppFEV_1$ of 40 to 90 at the time of screening. Some patients had $ppFEV_1$ levels that decreased to below 40 between the screening and baseline visits (≤4 weeks). In the pooled analysis, data from the two studies were pooled by dosing regimens.

Outcomes

For the pooled TRAFFIC and TRANSPORT study data, preplanned subgroup analyses of $ppFEV_1$ <40 versus ≥40 at baseline and $ppFEV_1$ <70 versus ≥70 at screening were performed for the primary endpoint and key secondary endpoints in a manner similar to that reported previously for the entire study cohort.[10] The primary endpoint was the absolute change from baseline in $ppFEV_1$ at week 24, calculated by averaging the mean absolute change at week 16 and the mean absolute change at week 24. Key secondary endpoints were: the relative change from baseline in $ppFEV_1$ at week 24

(calculated by averaging the mean values for weeks 16 and 24); the percentage of patients with at least a 5% relative increase from baseline in $ppFEV_1$ (response derived using average relative change at weeks 16 and 24); the absolute change from baseline in body mass index (BMI) at week 24; the absolute change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at week 24; and the number of PEx through week 24 (expressed as a rate over 48 weeks). In addition, post hoc subgroup analyses were performed for the absolute change from baseline in $ppFEV_1$ at each study visit, the percentage of patients with at least a 10% relative increase from baseline in $ppFEV_1$ (response derived using average relative change at weeks 16 and 24), the number of PEx requiring intravenous (IV) antibiotics, and the number of PEx requiring hospitalisation. Safety and tolerability were assessed by reports of adverse events (AEs) and by clinical laboratory parameters.

Statistical analyses

The efficacy population included all patients who were randomised and received at least one dose of study drug (full analysis set); patients were analysed according to the study group to which they were randomised. Pooled data were analysed for each subgroup separately, defined according to $ppFEV_1$ <40 and ≥40 at baseline and $ppFEV_1$ <70 and ≥70 at screening; these analyses were not powered statistically for efficacy comparisons between treatment groups. P values <0·05 were considered statistically significant and were not adjusted for multiple comparisons. The least squares (LS) means for the subgroup analysis of the absolute and relative changes from baseline in $ppFEV_1$ were calculated using a mixed-effects model for repeated measures (MMRM)

that included study, sex, age (<18 vs ≥18 years), treatment, visit, and treatment-by-visit interaction. The odds ratio versus placebo for the percentage of patients with at least a 5% and at least 10% relative increase from baseline in $ppFEV_1$ for each subgroup was estimated using the Cochran-Mantel-Haenszel test, stratified by study, baseline age (<18 vs ≥18 years), and sex. The LS means for the subgroup analysis of absolute change in BMI and CFQ-R respiratory domain were calculated using an MMRM model that included study, sex, age, treatment, visit, and treatment-by-visit interaction, plus the corresponding baseline as a covariate. The rate ratio of PEx events for each subgroup (ie, event rate per year for the treatment group vs that for the placebo group) was calculated using a negative binomial regression model that included study, treatment, sex, and age, with $\log_{(\text{time on study in years})}$ as an offset; 48 weeks was considered equivalent to 1 year for the analysis.

The safety analysis included all patients who received any amount of study drug and was based on actual treatment received. Patients who received medication from more than one treatment group during the studies were considered to be in the lower dose of the active treatment group.

Statistical analyses were performed using Statistical Analysis Software version 9·2 or higher. The studies were registered with ClinicalTrials.gov (NCT01807923 and NCT01807949).

Role of the funding source

The funder participated in the design of the protocol, performed the statistical analysis, and was involved in data interpretation. Medical writing as well as editorial support and coordination were provided by the funder. All authors had full access to the study data. JSE contributed to data interpretation and manuscript conception, writing and revision, and made the final decision to submit for publication.

Results

Of the 1122 patients who were randomised in the TRAFFIC and TRANSPORT studies, 1108 received at least one dose of study treatment (3 patients in the placebo group, 4 in the LUM 600 mg qd/IVA 250 mg q12h group, and 7 in the LUM 400 mg q12h/IVA 250 mg q12h group did not receive study drug). Three-hundred and forty two patients (30·9%) had a $ppFEV_1$ of ≥70 at screening, and 730 (65·9%) had a $ppFEV_1$ of <70 at screening. One thousand and sixteen patients (91·7%) had a $ppFEV_1$ of >40 at baseline; 81 (7·3%) had a $ppFEV_1$ level that decreased to <40 between the screening and baseline visits (range: 31·1-39·9). In the pooled data, treatment groups were well balanced across demographic and baseline characteristics, as reported previously.[10] Characteristics of the subgroups at baseline classified by $ppFEV_1$ <40 versus ≥40 and by $ppFEV_1$ <70 versus ≥70 are shown in Table 1. A high percentage of patients in each subgroup reported maintenance use of bronchodilators and multiple other CF treatments. The majority of patients in each subgroup completed 24 weeks of study treatment, including 78 of the 81 patients (96·3%) with severe lung dysfunction at baseline ($ppFEV_1$ <40). With respect to patients who received the LUM 400 mg q12h/IVA 250 mg q12h dose, there were 29 in the subgroup with $ppFEV_1$ <40 at

baseline, 336 in the subgroup with ppFEV$_1$ ≥40 at baseline, 245 in the subgroup with ppFEV$_1$ <70 at screening, and 114 in the subgroup with ppFEV$_1$ ≥70 at screening.

Significant improvements in the primary efficacy endpoint, absolute change from baseline in ppFEV$_1$ at week 24, were observed with both doses of LUM/IVA (LUM 600 mg qd/IVA 250 mg q12h and LUM 400 mg q12h/IVA 250 mg q12h) in the subgroup with ppFEV$_1$ <40 at baseline (LS mean difference versus placebo [95% confidence interval {CI}] was 3·7 (0·5-6·9) and 3.3 (0·2-6·4) percentage points, respectively [p<0·05]) and in the subgroup with ppFEV$_1$ ≥40 at baseline (3·3 (2·3-4·4) and 2·8 (1·7-3·8) percentage points, respectively [p<0·001]) (Table 2). Generally similar results favoring LUM/IVA over placebo were observed in subgroups with ppFEV$_1$ <70 and ≥70 at screening, although statistical significance was not reached in the ≥70 subgroup receiving LUM 400 mg q12h/IVA 250 mg q12h (Table 3). The absolute change versus placebo across all lung function subgroups ranged from 1·9-3·7 percentage points, consistent with differences observed in the overall population pooled from the two studies by dosing regimen (2·8-3·3 percentage points).[10] Figure 1 shows the absolute change from baseline in ppFEV$_1$ at each study visit throughout 24 weeks of treatment in subgroups defined by ppFEV$_1$. Improvements in ppFEV$_1$ were observed as early as day 15 and were sustained through week 24 with both LUM/IVA doses in these subgroups.

The differences between LUM/IVA and placebo with respect to relative change from baseline at week 24 in ppFEV$_1$ were consistent with results for the absolute change in ppFEV$_1$. Relative improvements in ppFEV$_1$ with LUM 600 mg qd/IVA 250 mg q12h and

LUM 400 mg q12h/IVA 250 mg q12h versus placebo (95% CI) were 9·9% (1·2-18·5) and 9·1% (0·7-17·4), respectively in the subgroup with baseline ppFEV$_1$ <40 (p<0·05) and 5·3% (3·5-7·1) and 4·5% (2·7-6·3), respectively in the subgroup with baseline ppFEV$_1$ ≥40 (p<0·001) (Table 2). Relative improvements in ppFEV$_1$ with both LUM/IVA doses versus placebo were also observed in the subgroups with screening ppFEV$_1$ <70 (6·0% (3·7-8·2) and 5·9% (3·6-8·2), respectively) and ≥70 (4·4% (1·5-7·4) and 2·5% (-0·5-5·5), respectively); once again, significance was not reached in the ≥70 subgroup receiving LUM 400 mg q12h/IVA 250 mg q12h (Table 3). The proportion of patients with ≥5% and ≥10% average relative increases from baseline at weeks 16 and 24 in ppFEV$_1$ was significantly higher with both LUM/IVA doses than with placebo in subgroups with ppFEV$_1$ ≥40 at baseline (p≤0·002) and ppFEV$_1$ <70 at screening (p<0·001) (Figure 2). Similar trends favoring LUM/IVA doses were observed in the other subgroups, but statistical significance was not reached in most comparisons in the smaller subgroup with baseline ppFEV$_1$ <40; significance was achieved for most comparisons in the subgroup with screening ppFEV$_1$ ≥70 (Figure 2).

On other clinical parameters, we observed generally consistent improvements across subgroups. The absolute change in BMI was statistically significant in most subgroups (Tables 2-3). Improvements in the CFQ-R respiratory domain score favoring LUM/IVA over placebo were observed in some of the larger subgroups, including those with ppFEV$_1$ ≥40 at both LUM/IVA doses (Tables 2-3), although variability on this measure was high, particularly in the subgroups with small patient numbers.

Treatment with LUM/IVA significantly reduced the number of PEx compared with placebo in most $ppFEV_1$ subgroups (Table 4). Additionally, trends toward fewer PEx events requiring IV antibiotic therapy and hospitalisations were observed in both LUM/IVA dose groups versus placebo across all lung function subgroups (Table 4).

The overall incidence of AEs in both LUM/IVA groups and in the placebo group was similar among patients with $ppFEV_1$ <40 and ≥40 at baseline and those with $ppFEV_1$ <70 and ≥70 at screening (Table 5). Because the incidence of AEs was similar between the two LUM/IVA dose groups, the safety data of the two dosing regimens were pooled. The most commonly reported AEs across all treatment groups were infective PEx of CF and cough. The incidence of certain respiratory AEs was greater in the pooled LUM/IVA group than in the placebo group in all subgroups; in patients with baseline $ppFEV_1$ <40, these AEs with higher incidence in the pooled LUM/IVA group than in placebo included cough (39·6% vs 25·0%), dyspnoea (26·4% vs 14·3%), and respiration abnormal (the Preferred Term for the verbatim term of chest tightness [7·5% vs 3·6%]). The incidence of dyspnoea and respiration abnormal was also greater in the pooled LUM/IVA group than in the placebo group in those with baseline $ppFEV_1$ ≥40 (13·0% vs 7·4% and 10·0% vs 6·2%, respectively), as well as in those with screening $ppFEV_1$ <70 and ≥70 (Table 5). Irrespective of lung function subgroup, respiratory AEs were associated with the initiation of treatment and usually resolved with continued treatment. The median time (min–max) to onset of the first AE of special interest of respiratory symptoms was 2 (1-170) days for the pooled LUM/IVA groups (n=738) and 43 (1-172) days for the placebo group (n=370). Generally similar results were observed across subgroups, with

the exception of a notably shorter time to onset of the first AE of special interest of respiratory symptoms among placebo-treated patients in the <40 subgroup. The median time (min–max) in the <40 subgroup was 1 (1-155) day for the pooled LUM/IVA groups (n=18) and 7 (2-43) days in the placebo group (n=5); in the ≥40 subgroup, the median time (min–max) was 2 (1-170) days for the pooled LUM/IVA groups (n=150) and 43 (1-172) days in the placebo group (n=46) .

With respect to baseline ppFEV$_1$ values, the incidence of dyspnoea was approximately two times higher in patients with ppFEV$_1$ <40 versus ≥40 in both the placebo group (14·3% vs 7·4%) and active treatment group (26·4% vs 13·0%), consistent with what might be expected for a population of patients with more severe lung dysfunction. The incidence of dyspnoea was also increased in patients with screening ppFEV$_1$ <70 versus ≥70 in both the placebo group (10·7% vs 2·8%) and active treatment group (17·0% vs 7·3%). The incidence of cough was greater in patients with baseline ppFEV$_1$ <40 versus ≥40 in the LUM/IVA group (39·6% vs 29·9%) but lower in the placebo group (25·0% vs 41·5%). The incidence of cough in patients with screening ppFEV$_1$ <70 versus ≥70 was generally similar in the both the placebo group (38·7% vs 43·1%) and LUM/IVA group (31·4% vs 29·2%). The proportion of patients who discontinued treatment because of AEs was small across all subgroups; such discontinuations occurred in 3·6% of patients (n=1) who received placebo and 0% who received LUM/IVA in the <40 subgroup, and in 1·5% of patients (n=5) who received placebo and 4·6% of patients (n=31) who received LUM/IVA in the ≥40 subgroup.

Discussion

This pooled analysis of data from the TRAFFIC and TRANSPORT studies shows that the efficacy and safety of LUM/IVA in patients with CF homozygous for the Phe508del *CFTR* mutation was similar across lung function subgroups, including $ppFEV_1$ <40 and ≥40 at baseline and $ppFEV_1$ <70 and ≥70 at screening.

The data in the subgroup with $ppFEV_1$ <40 at baseline were notable given the severity of lung function impairment in these patients ($ppFEV_1$ range of 31·1-39·9 percentage points). In this subgroup, the absolute improvement in lung function, as measured by $ppFEV_1$, from baseline at week 24 with both LUM/IVA doses compared with placebo ranged from 3·3 to 3·7 percentage points, which was similar to the improvement in lung function observed in those with $ppFEV_1$ ≥40 (2·8-3·3 percentage points) and in the overall study population.[10] Also notable were outcomes in patients whose $ppFEV_1$ was ≥70 at screening; lung function improvements in this subgroup were also generally consistent with the overall study population.[10]

Clinical improvements in BMI were also seen with both LUM/IVA doses compared with placebo; these were generally similar in magnitude across lung function subgroups. Furthermore, clinically meaningful reductions in PEx events were observed across lung function subgroups, including those with $ppFEV_1$ <40 at baseline and ≥70 at screening. Similarly, reductions in those events requiring the use of IV antibiotics and hospitalisation were observed across subgroups; the majority of these comparisons reached statistical significance. While the small sample size in some subgroups limits

the strength of our findings, the differences in the main outcome measures were statistically different.and It is encouragingthat the effect sizes are consistent with meaningful clinical benefit in these subgroups.

Using the respiratory domain of the CFQ-R, a CF-specific patient-reported outcome instrument,[13] significant improvements were noted in some of the subgroups with larger patient numbers with consistent trends in other subgroups, with the exception of the <40 subgroup treated with the LUM 400 mg q12h/IVA 250 mg q12h dose. A possible explanation for this finding could be related to AEs; however, variability on this measure was high, particularly in the smaller subgroups, which limited interpretation of these findings.

The side-effect profile of LUM/IVA therapy was acceptable in each lung function subgroup. The rates of discontinuation due to AEs were low across lung function subgroups. The incidence of certain respiratory AEs (such as dyspnoea) was higher in subgroups with more impaired lung function (eg, ppFEV$_1$ <40 versus ≥40) in both the placebo and LUM/IVA groups. The increased incidence of certain respiratory AEs in those with ppFEV$_1$ <40 versus ≥40 is consistent with the nature of CF in a population of patients with more severe lung dysfunction. The incidence of certain respiratory AEs was also higher in the active treatment groups versus placebo groups, notably in the subgroup with ppFEV$_1$ <40 at baseline (eg, dyspnoea and respiration abnormal, or chest tightness); when respiratory AEs were present, they were generally associated with the

initiation of treatment, irrespective of lung function impairment, and usually resolved with continued treatment.

It should be noted that these subgroup analyses were not powered statistically for efficacy comparisons between treatment groups. This is particularly important for subgroups with small numbers of patients, such as those with $ppFEV_1$ <40 at baseline. Nevertheless, the outcomes in patients with severe lung dysfunction were consistent with improvements observed in patients with $ppFEV_1$ ≥40 at baseline, suggesting a benefit of LUM/IVA combination therapy across a range of differing $ppFEV_1$ values. The generalizability of these findings to patients with severe lung dysfunction should be approached cautiously, as these trials were not designed to recruit patients with $ppFEV_1$ levels below 40. Perhaps, these patients may not fully reflect the profile of patients specifically recruited based on having $ppFEV_1$ levels <40. Prospective evaluation is needed to confirm the benefit of LUM/IVA therapy in this clinically important subgroup. Further, we consider the possibility that selection bias may have influenced the patients enrolled in the study, in particular in the <40 subgroup, as physicians may have been motivated to optimize the health of their patients whose lung function was near the eligibility cut off; while this would not be expected to influence efficacy outcomes due to the randomised nature of the trial, a potential impact on safety outcomes cannot be discounted.

Finally, it is important to bear in mind that the subgroup of patients with severe lung dysfunction included in this analysis had $ppFEV_1$ values ranging between 31·1 to 39·9

percentage points. Special attention may be needed in initiating patients with ppFEV$_1$ below 30 until further results are available. An open-label Phase 3b trial to assess the safety and efficacy of LUM/IVA combination therapy in patients with severe lung dysfunction is currently ongoing (ClinicalTrials.gov number, NCT02390219).

In conclusion, the results of these subgroup analyses of the Phase 3 TRAFFIC and TRANSPORT studies revealed generally consistent improvements across lung function subgroups, including those with ppFEV1 <40 and ≥70, suggesting that LUM/IVA combination therapy was generally well tolerated and benefits patients homozygous for the Phe508del *CFTR* mutation across a spectrum of lung function impairment.

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Author contributions

JSE contributed to the study design, collection, analysis, and interpretation of data, and drafting of the paper. BWR contributed to the study design, interpretation of data, and drafting of the paper. MPB contributed to the collection, analysis, and interpretation of data, and drafting of the paper. MWK contributed to the collection and interpretation of

data and drafting of the paper. XH contributed to the study design, analysis and interpretation of data, and drafting of the paper. GM contributed to the study design, collection, analysis, and interpretation of data. DW contributed to study design, analysis, and interpretation of data, and drafting of the paper. CEW contributed to the collection and interpretation of data, and critical review of the paper.

Declaration of interests

JSE reports speaker fees from Vertex Pharmaceuticals Incorporated, grants from Novartis and ProQR, and consultant fees from ProQR during the conduct of the study. BWR reports contract support from Aridis, Celtaxsys, Flatley Discover Lab LLV, KaloBios, Laurent Therapeutics, Nilvalis Therapeutics, Synedgen, and Vertex Pharmaceuticals Incorporated outside of the submitted work. MPB reports grants from Vertex Pharmaceuticals Incorporated during the conduct of the study. MWK reports grants, consultant fees, and travel support from Vertex Pharmaceuticals Incorporated during the conduct of the study; grants and travel support from the Cystic Fibrosis Foundation; consultant fees from Anthera, Chiesi, Digestive Care Inc, and Laurent; grants, consultant fees, and travel support from Genentech, Insmed, Novartis, PTC Therapeutics, and Vertex Pharmaceutical Incorporated; consultant fees and travel support from AbbVie, Celtaxsys, and Gilead; grants and consultant fees from Savara and KaloBios, outside of the submitted work. XH, GM, and DW are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. CEW reports receiving grant income on a per patient basis for conducting studies, consultant fees, and travel support from Vertex Pharmaceuticals Incorporated during

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Tables

Characteristics	Placebo overall (n=371)	LUM/IVA overall			
		$ppFEV_1$ <40* (n=53)	$ppFEV_1$ ≥40 (n=678)	$ppFEV_1$ <70 (n=527)	$ppFEV_1$ ≥70 (n=204)
Female, n (%)	181 (48·8)	31 (58·5)	331 (48·8)	269 (51·0)	93 (45·6)
Age, mean (range), years	25·4 (12-64)	27·3 (13-44)	24·7 (12-57)	26·3 (12-57)	21·0 (12-53)
$ppFEV_1$ at baseline, mean (range)	60·4 (33·9-99·8)	37·2 (31·1-39·9)	62·5 (40·0-96·5)	54·0 (31·1-69·8)	77·9 (70·0-96·5)
Body mass index (mg/kg^2), mean (range)	21·0 (14·1-32·2)	20·9 (16·1-31·4)	21·3 (14·2-35·1)	21·2 (14·2-35·1)	21·4 (14·6-29·8)
Chronic CF therapy use at baseline, n (%)					
Bronchodilators (any)	342 (92·2)	50 (94·3)	631 (93·1)	496 (94·1)	185 (90·7)
Dornase alfa	281 (75·7)	41 (77·4)	517 (76·3)	407 (77·2)	151 (74·0)
Inhaled antibiotic	258 (69·5)	33 (62·3)	421 (62·1)	351 (66·6)	103 (50·5)
Inhaled hypertonic saline	220 (59·3)	34 (64·2)	386 (56·9)	294 (55·8)	126 (61·8)
Inhaled corticosteroids	220 (59·3)	35 (66·0)	386 (56·9)	311 (59·0)	110 (53·9)

*Eighty-one patients (placebo, n=28; LUM/IVA, n=53) had $ppFEV_1$ that decreased to <40 between screening and baseline.

CF=cystic fibrosis; IVA=ivacaftor; LUM=lumacaftor; $ppFEV_1$=percent predicted forced expiratory volume in 1 second.

Table 1: Patient demographic and baseline characteristics

Parameter	Placebo		LUM 600 mg qd/IVA 250 mg q12h		LUM 400 mg q12h/IVA 250 mg q12h	
	ppFEV$_1$ at baseline*					
	<40 (n=28)	≥40 (n=338)	<40 (n=24)	≥40 (n=342)	<40 (n=29)	≥40 (n=336)
Absolute change in ppFEV$_1$						
Within group LS mean (SE)	0·4 (1·3)	-0·4 (0·4)	–	–	–	–
LS mean vs placebo (95% CI), percentage points†	–	–	3·7 (0·5-6·9)	3·3 (2·3-4·4)	3·3 (0·2-6·4)	2·8 (1·7-3·8)
p value	–	–	0·024	<0·001	0·036	<0·001
Relative change in ppFEV$_1$						
Within group LS mean (SE)	1·5 (3·4)	-0·2 (0·7)	–	–	–	–
LS mean vs placebo (95% CI), %†	–	–	9·9 (1·2-18·5)	5·3 (3·5-7·1)	9·1 (0·7-17·4)	4·5 (2·7-6·3)
p value	–	–	0·026	<0·001	0·034	<0·001
Relative increase of ≥5% from baseline in ppFEV$_1$‡						
Odds ratio vs placebo (95% CI)	–	–	2·4 (0·8-7·2)	3·1 (2·2-4·3)	1·7 (0·6-5·2)	2·3 (1·6-3·2)
p value	–	–	0·113	<0·001	0·331	<0·001
Body mass index						

Within group LS mean (SE)	0·1 (0·2)	0·1 (0·1)	–	–	–	–
LS mean vs placebo (95% CI), kg/m^2	–	–	0·6 (0·1-1·2)	0·3 (0·1-0·4)	0·3 (-0·2-0·8)	0·2 (0·1-0·4)
p value	–	–	0·023	<0·001	0·261	0·001
CFQ-R respiratory domain						
Within group LS mean (SE)	5·8 (3·2)	0·9 (0·9)	–	–	–	–
LS mean vs placebo (95% CI), points	–	–	3·3 (-5·2-11·7)	3·3 (1·0-5·7)	-4·2 (-12·0-3·7)	2·9 (0·5-5·3)
p value	–	–	0·446	0·006	0·298	0·017

*Eighty-one patients had $ppFEV_1$ levels that decreased to <40 between screening and baseline.

†Assessed by averaging the mean values from weeks 16 and 24, as prespecified in the statistical analysis plan.

‡Average relative increase from baseline at weeks 16 and 24.

CFQ-R=Cystic Fibrosis Questionnaire-Revised; CI=confidence interval; IVA=ivacaftor; LUM=lumacaftor; LS=least squares; $ppFEV_1$=percent predicted forced expiratory volume in 1 second; SE=standard error; q12h=every 12 hours; qd=every day.

Table 2: Efficacy results after treatment with LUM/IVA for 24 weeks in patients with $ppFEV_1$ <40 vs ≥40 at baseline

Parameter	Placebo		LUM 600 mg qd/IVA 250 mg q12h		LUM 400 mg q12h/IVA 250 mg q12h	
	ppFEV$_1$ at screening*					
	<70 (n=244)	≥70 (n=109)	<70 (n=241)	≥70 (n=119)	<70 (n=245)	≥70 (n=114)
Absolute change in ppFEV$_1$						
Within group LS mean (SE)	-0·5 (0·4)	0·1 (0·8)	–	–	–	–
LS mean vs placebo (95% CI), percentage points†	–	–	3·3 (2·1-4·4)	3·3 (1·3-5·4)	3·3 (2·1-4·4)	1·9 (-0·2-4·0)
p value	–	–	<0·001	0·002	<0·001	0·079
Relative change in ppFEV$_1$						
Within group LS mean (SE)	-0·3 (0·9)	0·7 (1·1)	–	–	–	–
LS mean vs placebo (95% CI), %†	–	–	6·0 (3·7-8·2)	4·4 (1·5-7·4)	5·9 (3·6-8·2)	2·5 (-0·5-5·5)
p value	–	–	<0·001	0·003	<0·001	0·103
Relative increase of ≥5% from baseline in ppFEV$_1$‡						
Odds ratio vs placebo (95% CI)	–	–	2·5 (1·7-3·7)	3·8 (2·1-6·8)	2·4 (1·6-3·5)	1·9 (1·0-3·4)
p value	–	–	<0·001	<0·001	<0·001	0·045

Body mass index						
Within group LS mean (SE)	0·1 (0·1)	0·1 (0·1)	–	–	–	–
LS mean vs placebo (95% CI), kg/m^2	–	–	0·2 (0·0-0·4)	0·4 (0·2-0·7)	0·2 (0·0-0·3)	0·3 (0·1-0·6)
p value	–	–	0·017	<0·001	0·041	0·006
CFQ-R respiratory domain						
Within group LS mean (SE)	1·5 (1·1)	1·7 (1·4)	–	–	–	–
LS mean vs placebo (95% CI), points	–	–	4·1 (1·3-6·9)	1·9 (-1·9-5·7)	1·9 (-0·9-4·7)	3·6 (-0·3-7·4)
p value	–	–	0·005	0·326	0·184	0·071

*Eighty-one patients had $ppFEV_1$ that decreased to <40 between screening and baseline.

†Assessed by averaging the mean values from weeks 16 and 24, according to the prespecified statistical analysis plan.

‡Average relative increase from baseline at weeks 16 and 24.

CFQ-R=Cystic Fibrosis Questionnaire-Revised; CI=confidence interval; IVA=ivacaftor; LUM=lumacaftor; LS=least squares; $ppFEV_1$=percent predicted forced expiratory volume in 1 second; SE=standard error; q12h=every 12 hours; qd=every day.

Table 3: Efficacy results after treatment with LUM/IVA for 24 weeks in patients with $ppFEV_1$ <70 vs ≥70 at screening

Rate ratio vs placebo (95% CI)	LUM 600 mg qd/IVA 250 mg q12h		LUM 400 mg q12h/IVA 250 mg q12h	
	ppFEV$_1$ at baseline			
	<40 (n=24)*	≥40 (n=342)	<40 (n=29)*	≥40 (n=336)
Pulmonary exacerbation events	0·47 (0·24-0·93)	0·73 (0·58-0·92)	0·59 (0·33-1·05)	0·61 (0·48-0·77)
p value	0·030	0·007	0·074	<0·001
Events requiring IV antibiotic therapy	0·41 (0·17-0·98)	0·57 (0·43-0·77)	0·56 (0·27-1·17)	0·42 (0·30-0·58)
p value	0·046	<0·001	0·122	<0·001
Events requiring hospitalisation	0·43 (0·14-1·33)	0·63 (0·44-0·89)	0·67 (0·27-1·65)	0·36 (0·23-0·54)
p value	0·142	0·009	0·382	<0·001
	ppFEV$_1$ at screening			
	<70 (n=241)	≥70 (n=119)	<70 (n=245)	≥70 (n=114)
Pulmonary exacerbation events	0·74 (0·57-0·95)	0·55 (0·35-0·85)	0·65 (0·50-0·84)	0·51 (0·32-0·80)
p value	0·018	0·007	0·001	0·003
Events requiring IV antibiotic therapy	0·53 (0·39-0·73)	0·53 (0·27-1·01)	0·49 (0·36-0·68)	0·22 (0·09-0·55)

p value	<0·001	0·052	<0·001	0·001
Events requiring hospitalisation	0·59 (0·40-0·85)	0·53 (0·27-1·06)	0·48 (0·32-0·71)	0·09 (0·02-0·37)
p value	0·005	0·072	<0·001	0·001

*Eighty-one patients had ppFEV$_1$ that decreased to <40 between screening and baseline.

CI=confidence interval; IV=intravenous; IVA=ivacaftor; LUM=lumacaftor; q12h=every 12 hours; qd=every day.

Table 4: Pulmonary exacerbation events through week 24 by ppFEV$_1$ subgroup and treatment group

	Placebo		LUM/IVA*		Placebo		LUM/IVA*	
	ppFEV$_1$ at baseline				ppFEV$_1$ at screening			
Variable, n (%)	<40 (n=28)	≥40 (n=337)	<40 (n=53)	≥40 (n=679)	<70 (n=243)	≥70 (n=109)	<70 (n=487)	≥70 (n=233)
Patients who experienced any AE	28 (100)	322 (95·5)	52 (98·1)	649 (95·6)	235 (96·7)	102 (93·6)	466 (95·7)	224 (96·1)
AEs reported in ≥10% of patients in any subgroup of placebo or total LUM/IVA								
Infective PEx of CF	20 (71·4)	162 (48·1)	27 (50·9)	248 (36·5)	125 (51·4)	53 (48·6)	211 (43·3)	59 (25·3)
Cough	7 (25·0)	140 (41·5)	21 (39·6)	203 (29·9)	94 (38·7)	47 (43·1)	153 (31·4)	68 (29·2)
Dyspnoea	4 (14·3)	25 (7·4)	14 (26·4)	88 (13·0)	26 (10·7)	3 (2·8)	83 (17·0)	17 (7·3)
Sputum increased	8 (28·6)	62 (18·4)	13 (24·5)	94 (13·8)	49 (20·2)	18 (16·5)	80 (16·4)	25 (10·7)
Headache	5 (17·9)	52 (15·4)	10 (18·9)	103 (15·2)	42 (17·3)	14 (12·8)	74 (15·2)	36 (15·5)
Pyrexia	5 (17·9)	29 (8·6)	8 (15·1)	59 (8·7)	28 (11·5)	6 (5·5)	51 (10·5)	15 (6·4)
Diarrhoea	2 (7·1)	29 (8·6)	7 (13·2)	73 (10·8)	19 (7·8)	10 (9·2)	62 (12·7)	16 (6·9)
Nausea	3 (10·7)	25 (7·4)	7 (13·2)	67 (9·9)	18 (7·4)	9 (8·3)	56 (11·5)	17 (7·3)

Fatigue	2 (7·1)	27 (8·0)	6 (11·3)	57 (8·4)	21 (8·6)	7 (6·4)	48 (9·9)	15 (6·4)
Haemoptysis	7 (25·0)	43 (12·8)	6 (11·3)	95 (14·0)	42 (17·3)	8 (7·3)	81 (16·6)	18 (7·7)
Nasopharyngitis	2 (7·1)	37 (11·0)	6 (11·3)	65 (9·6)	30 (12·3)	8 (7·3)	49 (10·1)	20 (8·6)
Oropharyngeal pain	1 (3·6)	29 (8·6)	6 (11·3)	61 (9·0)	17 (7·0)	11 (10·1)	43 (8·8)	24 (10·3)
URTI	0 (0)	19 (5·6)	6 (11·3)	53 (7·8)	12 (4·9)	5 (4·6)	39 (8·0)	18 (7·7)
Nasal congestion	1 (3·6)	43 (12·8)	5 (9·4)	52 (7·7)	22 (9·1)	21 (19·3)	34 (7·0)	23 (9·9)
Respiration abnormal	1 (3·6)	21 (6·2)	4 (7·5)	68 (10·0)	19 (7·8)	2 (1·8)	49 (10·1)	22 (9·4)
Blood creatinine phosphokinase increased	1 (3·6)	19 (5·6)	2 (3·8)	39 (5·7)	7 (2·9)	12 (11·0)	24 (4·9)	16 (6·9)
Viral URTI	4 (14·3)	20 (5·9)	2 (3·8)	48 (7·1)	15 (6·2)	8 (7·3)	34 (7·0)	16 (6·9)

*Pooled data for the LUM 600 mg qd/IVA 250 mg q12h and LUM 400 mg q12h/IVA 250 mg q12h groups.

AE=adverse event; CF=cystic fibrosis; IVA=ivacaftor; LUM=lumacaftor; PEx=pulmonary exacerbation; ppFEV$_1$=percent predicted forced expiratory volume in 1 second; URTI=upper respiratory tract infection.

Table 5: Summary of treatment-emergent adverse events

Figures

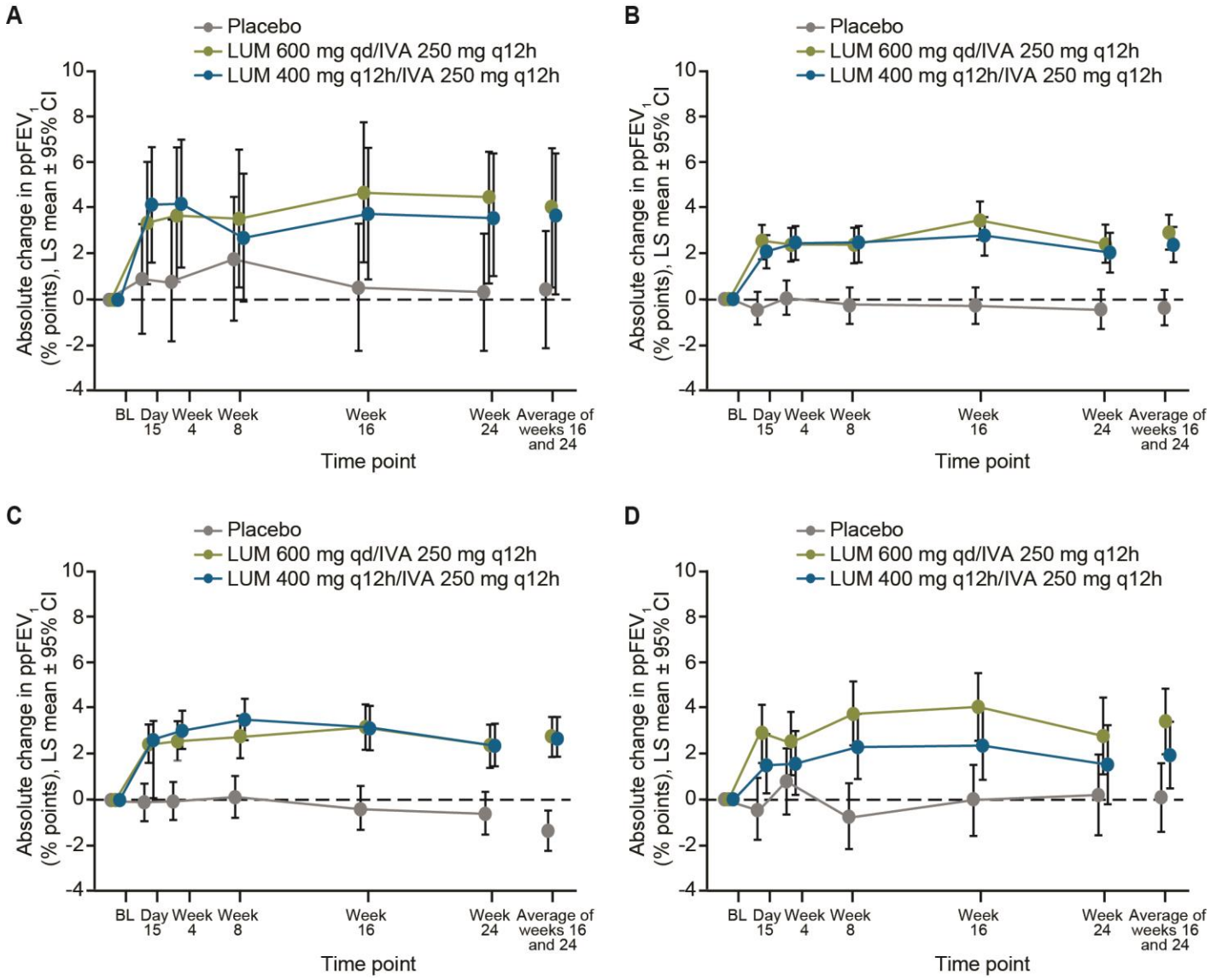

A
B
C
D
Placebo
LUM 600 mg qd/IVA 250 mg q12h
LUM 400 mg q12h/IVA 250 mg q12h
Absolute change in ppFEV1 (% points), LS mean ± 95% CI
10
8
6
4
2
0
-2
-4
BL
Day 15
Week 4
Week 8
Week 16
Week 24
Average of weeks 16 and 24
Time point

Figure 1

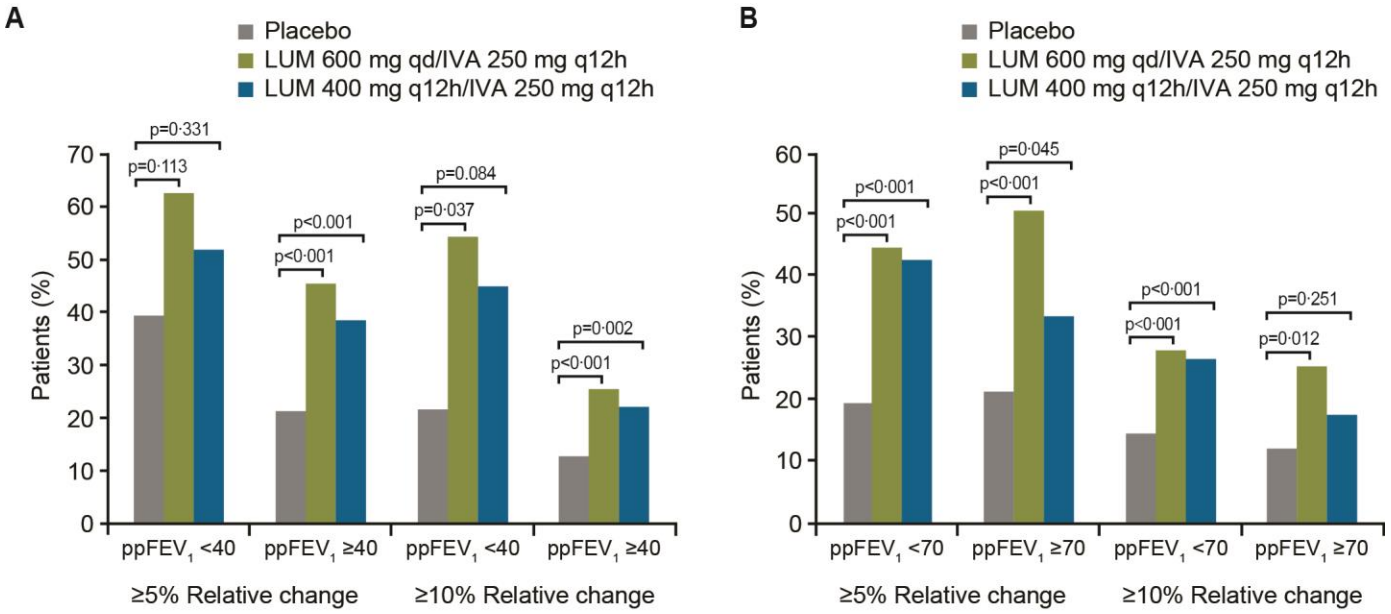

A
Placebo
LUM 600 mg qd/IVA 250 mg q12h
LUM 400 mg q12h/IVA 250 mg q12h
Patients (%)
p=0·331
p=0·113
p<0.001
p<0·001
p=0.084
p=0·037
p=0·002
p<0·001
ppFEV1 <40
ppFEV1 ≥40
ppFEV1 <40
ppFEV1 ≥40
≥5% Relative change
≥10% Relative change
B
Placebo
LUM 600 mg qd/IVA 250 mg q12h
LUM 400 mg q12h/IVA 250 mg q12h
Patients (%)
p<0·001
p<0·001
p=0·045
p<0·001
p<0·001
p<0·001
p=0·251
p=0·012
ppFEV1 <70
ppFEV1 ≥70
ppFEV1 <70
ppFEV1 ≥70
≥5% Relative change
≥10% Relative change

Figure 2

Figure Legends

Figure 1: Absolute change from baseline in $ppFEV_1$ at each study visit for patients with baseline $ppFEV_1$ <40 (A) or ≥40 (B), and for patients with screening $ppFEV_1$ <70 (C) or ≥70 (D)

BL=baseline; CI=confidence interval; IVA=ivacaftor; LUM=lumacaftor; LS=least squares; $ppFEV_1$=percent predicted forced expiratory volume in 1 second; q12h=once every 12 hours; qd=once daily.

Figure 2: Percentage of patients with ≥5% and ≥10% average relative increases from baseline in $ppFEV_1$ at weeks 16 and 24 in patients with $ppFEV_1$ <40 or ≥40 at baseline (A) and $ppFEV_1$ <70 or ≥70 at screening (B)

IVA=ivacaftor; LUM=lumacaftor; $ppFEV_1$=percent predicted forced expiratory volume in 1 second; q12h=once every 12 hours; qd=once daily.

Supplementary Information

Study design and patients

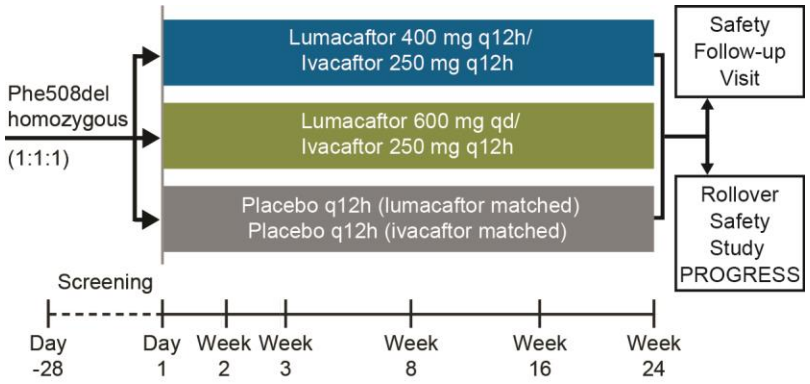
The TRAFFIC and TRANSPORT studies were Phase 3, multinational, randomised, double-blind, placebo-controlled, parallel-group studies conducted from April 2013 through April 2014.[1] The study protocols were identical except that ambulatory electrocardiography was measured only in the TRAFFIC study, and pharmacokinetic assessments were made in a subgroup of adolescent patients only in the TRANSPORT study.

Key inclusion criteria were age 12 years or older with a confirmed diagnosis of cystic fibrosis (CF), homozygous for the Phe508del *CFTR* mutation, a percent predicted forced expiratory volume in 1 second ($ppFEV_1$) of 40 to 90 at the time of screening, stable disease, and a willingness to remain on a specified CF treatment regimen for 24 weeks. Some patients had $ppFEV_1$ levels that reduced to below 40 between the screening and baseline visits (≤4 weeks). Key exclusion criteria were an acute upper or lower respiratory tract infection or change in therapy (including antibiotics) for pulmonary disease occurring within 4 weeks before the first dose of study drug, colonization with organisms associated with a more rapid decline in pulmonary status (eg, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*), history of solid organ or haematologic transplantation, or use of strong inhibitors or moderate or strong inducers of cytochrome P450 3A within 14 days before the first dose of study drug.

Procedures

Patients were randomly assigned in a 1:1:1 ratio to treatment with LUM 600 mg qd/IVA 250 mg q12h, LUM 400 mg q12h/IVA 250 mg q12h, or matched placebo q12h, stratified by age (<18 vs ≥18 years), sex, and $ppFEV_1$ at screening (<70 vs ≥70). Patients continued to take their prestudy medications throughout the study period. The study design schematic is shown in Supplementary Figure 1. Patients initiated study treatment within 4 weeks of screening; clinic visits during the 24-week treatment period were scheduled on days 1 (baseline) and 15, and at weeks 4, 8, 16, and 24. Patients who completed all visits during the treatment period, regardless of whether or not they discontinued study treatment, were eligible to enrol in a treatment or observational cohort of a rollover extension study (PROGRESS; ClinicalTrials.gov number, NCT01931839). A safety follow-up visit was scheduled at 4 weeks after completion of the week 24 visit but was not required for patients who chose to enrol in the extension study.

Supplemental Figure 1: TRAFFIC and TRANSPORT study design[1]


Phe508del
homozygous
(1:1:1)
Lumacaftor 400 mg q12h/
Ivacaftor 250 mg q12h
Lumacaftor 600 mg qd/
Ivacaftor 250 mg q12h
Placebo q12h (lumacaftor matched)
Placebo q12h (ivacaftor matched)
Safety
Follow-up
Visit
Rollover
Safety
Study
PROGRESS
Screening
Day
-28
Day
1
Week
2
Week
3
Week
8
Week
16
Week
24

Supplemental Table 1: Patient demographic and baseline characteristics

Characteristics	Placebo		LUM/IVA overall		Placebo		LUM/IVA overall	
	$ppFEV_1$ <40* **(n=28)**	**$ppFEV_1$ ≥40** **(n=338)**	**$ppFEV_1$ <40*** **(n=53)**	**$ppFEV_1$ ≥40** **(n=678)**	**$ppFEV_1$ <70** **(n=266)**	**$ppFEV_1$ ≥70** **(n=100)**	**$ppFEV_1$ <70** **(n=527)**	**$ppFEV_1$ ≥70** **(n=204)**
Female, n (%)	13 (46·4)	167 (49·4)	31 (58·5)	331 (48·8)	136 (51·1)	44 (44·0)	269 (51·0)	93 (45·6)
Age, mean (range), years	30.3 (14-55)	25.0 (12-64)	27·3 (13-44)	24·7 (12-57)	26·9 (12-64)	21·5 (12-50)	26·3 (12-57)	21·0 (12-53)
$ppFEV_1$ at baseline, mean (range)	37·4 (33·9-39·9)	62.3 (40·0-99·8)	37·2 (31·1-39·9)	62·5 (40·0-96·5)	54·0 (33·9-69·8)	77·6 (70·0-99·8)	54·0 (31·1-69·8)	77·9 (70·0-96·5)
Body mass index (mg/kg^2), mean (range)	20·3 (15·8-25·0)	21.1 (14·1-32·2)	20·9 (16·1-31·4)	21·3 (14·2-35·1)	20·9 (14·1-30·8)	21·3 (14·4-32·2)	21·2 (14·2-35·1)	21·4 (14·6-29·8)
Chronic CF therapy use at baseline, n (%)								
Bronchodilators (any)	27 (96·4)	311 (92·0)	50 (94·3)	631 (93·1)	247 (92·9)	91 (91·0)	496 (94·1)	185 (90·7)
Dornase alfa	23 (82·1)	253 (74·9)	41 (77·4)	517 (76·3)	203 (76·3)	73 (73·0)	407 (77·2)	151 (74·0)
Inhaled antibiotic	23 (82·1)	231 (68·3)	33 (62·3)	421 (62·1)	195 (73·3)	59 (59.0)	351 (66·6)	103 (50·5)

Inhaled hypertonic saline	15 (53·6)	204 (60·4)	34 (64·2)	386 (56·9)	151 (56·8)	68 (68·0)	294 (55·8)	126 (61·8)
Inhaled corticosteroids	19 (67·9)	200 (59·2)	35 (66·0)	386 (56·9)	171 (64·3)	48 (48·0)	311 (59·0)	110 (53·9)

Reference

1. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del *CFTR*. *N Engl J Med* 2015; **373:** 220-31.