Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for *F508del-CFTR*: a randomised, placebo-controlled, phase 3 trial

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Summary

Background Lumacaftor and ivacaftor combination treatment showed efficacy in patients aged 12 years or older with cystic fibrosis homozygous for *F508del-cystic fibrosis transmembrane conductance regulator* (*CFTR*) in placebo-controlled studies and patients aged 6–11 years with cystic fibrosis homozygous for *F508del-CFTR* in an open-label study. We report efficacy and safety of lumacaftor and ivacaftor in patients with cystic fibrosis aged 6–11 years homozygous for *F508del-CFTR*.

Methods In this phase 3, randomised, double-blind, placebo-controlled, multicentre study, patients were enrolled at 54 hospitals and medical centres in nine countries (the USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK). Eligible patients weighed at least 15 kg, with a confirmed diagnosis of cystic fibrosis, percent predicted forced expiratory volume in 1 s (FEV_1) of 70 or more, and lung clearance index$_{2·5}$ ($LCI_{2·5}$) of 7·5 or more at screening (values less than these thresholds were permitted at day 1). All patients were tested for *CFTR* genotype at screening; eligible patients had to have the *F508del-CFTR* mutation on both alleles. Exclusion criteria included any comorbidity or laboratory abnormality that might confound the study results or pose additional risk to the patient. Patients were stratified by weight (<25 kg *vs* ≥25 kg) and $ppFEV_1$ severity (<90 *vs* ≥90) determined at the screening visit, and randomly assigned 1:1 to treatment using an interactive web response system to receive 200 mg lumacaftor and 250 mg ivacaftor every 12 hours or placebo for 24 weeks. Patients, all site personnel including the investigator and the site monitor, and the study team were blinded, with the exception of site personnel needing this information in the event of medical emergency or pregnancy and patient safety and regulatory affairs personnel to meet serious adverse event reporting requirements. The primary endpoint was the mean absolute change in $LCI_{2·5}$ from all study visits up to and including week 24. All randomly assigned patients who were exposed to any amount of study drug, with treatment assignment as assigned were included in primary and other efficacy analyses. All patients who were exposed to any amount of study drug, with treatment assignment as treated, were included in the safety analysis. This study was registered with ClinicalTrials.gov, number NCT02514473.

Findings Between July 23, 2015, and Sept 20, 2016, a total of 206 patients were enrolled and randomly assigned to receive lumacaftor and ivacaftor (n=104) or placebo (n=102). Two randomly assigned patients were never dosed with study drug (one in the placebo arm due to ineligibility arising from a streptococcal throat infection and one in the lumacaftor and ivacaftor arm due to withdrawal based on refusal to provide blood tests) and were not included in the analyses. 103 patients received at least one dose of lumacaftor and ivacaftor and 101 patients received at least one dose of placebo. For the primary endpoint, the average absolute change in $LCI_{2·5}$ from baseline over all study visits up to and including the week 24 visit, least squares mean difference was –1·09 units (95% CI –1·43 to –0·75, p<0·0001) for lumacaftor and ivacaftor versus placebo. For the key secondary endpoint of sweat chloride concentration, the least squares mean difference versus placebo was –20·8 mmol/L (95% CI –23·4 to –18·2, average absolute change at day 15/week 4; p<0·0001). The least squares mean difference compared with placebo in absolute change in $ppFEV_1$ from all study visits until week 24 was 2·4 (95% CI 0·4–4·4, p=0·0182). 196 (96%) of 204 patients reported adverse events, most of which were mild (87 [43%]) or moderate (98 [48%]). Treatment was discontinued due to adverse events in three (3%) of 103 patients in the lumacaftor and ivacaftor group and two (2%) of 101 patients in the placebo group. Serious adverse events were reported in 13 (13%) of 103 patients in the lumacaftor and ivacaftor group and 11 (11%) of 101 patients in the placebo group.

Interpretation Treatment with lumacaftor and ivacaftor was associated with statistically significant improvements in lung function, as measured by $LCI_{2·5}$ and $ppFEV_1$, versus placebo in patients aged 6–11 years with cystic fibrosis homozygous for *F508del-CFTR*. The overall safety profile was consistent with previous phase 3 studies of lumacaftor and ivacaftor.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Feb 6, 2017, with the terms "ivacaftor" or "VX-770" and "lumacaftor" or "VX-809", with no restrictions on publication date or language. We identified four relevant clinical studies: one combined report of two phase 3 trials in patients aged 12 years or older with cystic fibrosis and homozygous for *F508del-CFTR* (TRAFFIC and TRANSPORT); a phase 3 extension study of TRAFFIC and TRANSPORT (PROGRESS); and an open-label, phase 3 study in patients aged 6–11 years with cystic fibrosis and homozygous for *F508del-CFTR*. Lumacaftor and ivacaftor are modulators of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. Combination therapy with lumacaftor and ivacaftor for 24 weeks in patients aged 12 years and older improved lung function and nutritional status, and decreased rates of pulmonary exacerbation, with an acceptable safety profile in the TRAFFIC and TRANSPORT trials. In the 96-week extension study (PROGRESS), the safety profile remained consistent, with benefits of lumacaftor and ivacaftor therapy being observed up to 120 weeks of treatment. Lumacaftor and ivacaftor treatment was also well tolerated over 24 weeks in younger patients with cystic fibrosis (aged 6–11 years) and homozygous for *F508del-CFTR* in an open-label, phase 3 study.

Added value of this study

In this phase 3, randomised, placebo-controlled trial (VX14-809-109), the efficacy of lumacaftor and ivacaftor combination therapy in patients aged 6–11 years with cystic fibrosis homozygous for the *F508del-CFTR* mutation was further assessed. Lung function in this paediatric population was measured by lung clearance index ($LCI_{2·5}$), a sensitive measure of ventilation inhomogeneity, and spirometry (percent predicted forced expiratory volume in 1 s [$ppFEV_1$]). Pharmacodynamic effect on CFTR function was established by assessment of sweat chloride concentration. $LCI_{2·5}$ and sweat chloride concentration improved significantly (ie, decreased) in the lumacaftor and ivacaftor group versus the placebo group. A significant treatment difference favouring lumacaftor and ivacaftor over placebo was also observed for $ppFEV_1$. The safety findings were consistent with those reported previously in young patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation.

Implications of all the available evidence

Significant improvements in lung function with lumacaftor and ivacaftor treatment were seen when measured by absolute change from baseline in $LCI_{2·5}$ relative to placebo treatment. Sweat chloride concentration also improved significantly (ie, decreased), thus providing a mechanistic CFTR biomarker of modulator efficacy. This phase 3 trial provides rigorous evidence for efficacy with lumacaftor and ivacaftor in the paediatric population at the early stages of disease and is among the first to use $LCI_{2·5}$ as a primary endpoint.

Introduction

Cystic fibrosis is a chronic, genetic disease characterised by loss of lung function, poor nutritional status, pulmonary exacerbations, and respiratory failure.[1] The disease is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an ion channel in the apical membrane of epithelial cells that conducts chloride ions and helps modulate bicarbonate ion transport.[2,3] Defective CFTR protein arises from mutations in the *CFTR* gene,[4] the most common being the *F508del* mutation, for which approximately 38% of the global cystic fibrosis population is homozygous.[5] The *F508del-CFTR* mutation affects processing and trafficking of the CFTR protein such that most is targeted for degradation before reaching the cell surface.[6] F508del-CFTR protein expressed at the apical membrane is usually unstable and functionally defective.[7,8]

Therapies directly targeting CFTR function have been developed, including ivacaftor, a CFTR potentiator that has been shown to increase channel open probability of mutant CFTR in vitro.[9] Delivery of CFTR protein to the cell surface can be increased by lumacaftor, a CFTR corrector that improves the processing and trafficking of F508del-CFTR protein.[10] Lumacaftor in combination with ivacaftor has greater effects than either agent alone, both in vitro and clinically in specific cystic fibrosis genotypes.[9–12] Combination treatment for 24 weeks improved lung function, reduced frequency of cystic fibrosis-related pulmonary exacerbations, and improved body-mass index (BMI) in two large phase 3 studies (TRAFFIC and TRANSPORT) in patients aged 12 years or older with cystic fibrosis and homozygous for *F508del-CFTR*.[12] In an open-label phase 3 study,[13] treatment with lumacaftor and ivacaftor was well tolerated over 24 weeks in patients aged 6–11 years homozygous for *F508del-CFTR*, with a safety profile similar to that seen in older patients. After treatment initiation, sweat chloride concentration rapidly decreased in the trial population of this study,[13] returning to baseline after discontinuation of therapy. Although statistically significant improvements in percent predicted forced expiratory volume in 1 s ($ppFEV_1$) were not observed in this population with generally preserved spirometric measures of lung function, ventilation inhomogeneity measured by the lung clearance index ($LCI_{2·5}$; number of lung volume turnovers required to reach 2·5% of starting tracer gas concentration), BMI *Z* score, and quality of life measures improved significantly. It is not uncommon for patients in this age group to have normal spirometry,[14] even when structural abnormalities can be

observed with high-resolution computed tomography[15] and hyperpolarised gas MRI[16,17] and LCI, which measures small airway disease, shows impaired ventilation.[18,19]

We designed this phase 3 study to further investigate the efficacy and safety of lumacaftor in combination with ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for the *F508del-CFTR* mutation. $LCI_{2·5}$ was chosen as the primary endpoint based on knowledge that it is a sensitive measure of lung function[20] in this younger population.

Methods

Study design and participants

This phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre study was done in patients aged 6–11 years with cystic fibrosis who were homozygous for the *F508del-CFTR* mutation (appendix). The study protocol, informed consent, and other necessary documents were approved by an independent ethics committee or institutional review board for each study site before initiation. This study was done in accordance with good clinical practice as described in the International Conference on Harmonisation Guideline E6, Good Clinical Practice, Consolidated Guidance (April, 1996). A total of 54 study sites (hospitals and medical centres) from the USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK participated in the trial.

Eligible patients were aged 6–11 years and weighed at least 15 kg, with a confirmed diagnosis of cystic fibrosis, $ppFEV_1$ of 70 or more, and $LCI_{2·5}$ of 7·5 or more (the upper limit of normal in this age group[21]) at screening (values less than these thresholds were permitted at day 1). Treatment was initiated within 28 days of screening. All patients were tested for *CFTR* genotype at screening; eligible patients had to have the *F508del-CFTR* mutation on both alleles. All enrolled patients and their parent or legal guardian provided written informed consent.

Patients were excluded if they had a comorbidity that might pose additional risk or confound study results (eg, history of cirrhosis with portal hypertension, history of risk factors for torsades de pointes), clinically significant abnormalities (haemoglobin <10 g/dL, abnormal liver or renal function), acute upper or lower respiratory infection, pulmonary exacerbation or changes in therapy for pulmonary disease within 28 days before day 1 of the study, or a history of solid organ or haematological transplantation.

Randomisation and masking

Patients were stratified by weight (<25 kg *vs* ≥25 kg) and $ppFEV_1$ severity (<90 *vs* ≥90), both determined at the screening visit, and then randomly assigned (1:1) to lumacaftor 200 mg every 12 hours in combination with ivacaftor 250 mg every 12 hours or matched placebo (appendix). Random assignment was determined using an interactive web response system (IWRS), and stratification influenced assignment such that groups were to be balanced for each stratification criterion: within each stratum, the IWRS randomly assigned patients to one of the two treatment groups. Randomisation blocks were assigned within stratum. Randomisation code for the IWRS was prepared by an external qualified randomisation vendor, who reviewed the final randomisation list and transferred it directly to the IWRS vendor. The randomisation vendor had no other involvement in the trial. The sponsor study team, including study biostatistician, had no access to the final live unblinded randomisation list during the study conduct. Blinding was achieved by using placebo tablets visually identical to the test product.

Procedures

Film-coated, fixed-dose combination tablets containing 100 mg lumacaftor and 125 mg ivacaftor or matching placebo were administered orally (2 tablets every 12 hours) under parental supervision for 24 weeks of treatment. All study visits were scheduled relative to the day 1 visit, eg, the week 8 (+/–5 days) visit would occur after 8 weeks of study drug administration was completed (day 57, the start of week 9). At study visits at day 1 and 15, and weeks 4, 16, and 24 (appendix), $LCI_{2·5}$ was measured by multiple breath N_2 washout[22,23] (Exhalyzer® D, EcoMedics AG, Duernen, Switzerland). During this test, a tracer gas (N_2) undergoes washout from the lungs while the patient breathes 100% O_2. $LCI_{2·5}$ represents the number of lung volume turnovers required to reduce the tracer gas concentration to 2·5% of its initial concentration. A reduction in $LCI_{2·5}$ indicates improvement in ventilation inhomogeneity. $LCI_{2·5}$ values from visits with at least two acceptable trials were reported. Details on multiple-breath washout training, certification, and quality control are included in the appendix. Spirometry (all study visits) and sweat chloride concentration (day 1 and 15, and weeks 4, 16, and 24) were also measured, and the Cystic Fibrosis Questionnaire-Revised (CFQ-R)[24] was completed before the morning dose of study drug at all clinical visits. The version and format of the CFQ-R was based on age at day 1. Fecal elastase-1 (FE-1) measurements were recorded at baseline and week 24. Safety assessments included adverse events (as determined by the investigator), clinical laboratory assessments, vital signs, pulse oximetry, electrocardiograms, physical examinations, ophthalmologic examinations, and spirometry (including serial post-dose measurements). At the week 24 visit, patients who completed study drug treatment and visits in the treatment period were offered the option of enrolment in an open-label 96-week rollover study (VX15-809-110, NCT02544451; appendix). A safety follow-up visit

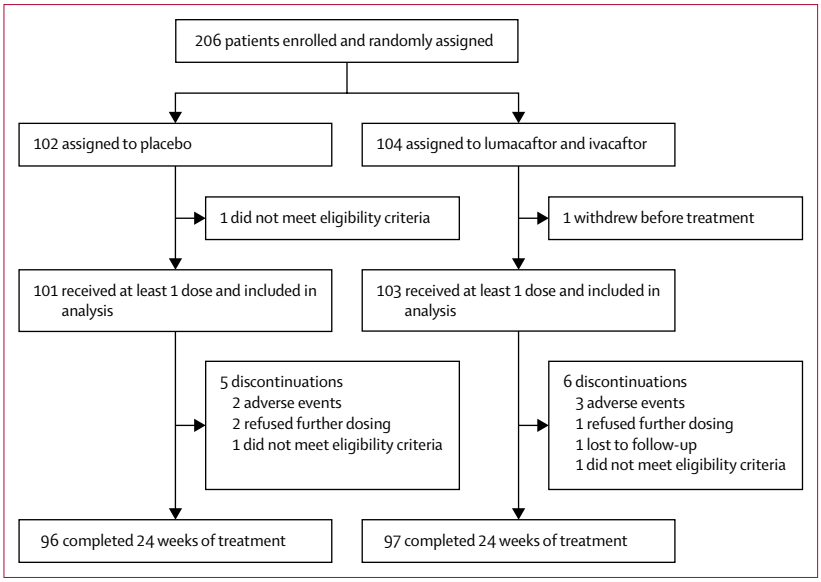

Figure 1: **Trial profile**
Additional patients who were screened and not enrolled due to not meeting exclusion or inclusion criteria were not captured in the study database.

occurred 4 weeks (+/–7 days) after the last dose; this visit was not required for patients who enrolled in the rollover study within 28 days after last dose of study drug.

Outcomes

Efficacy and safety were assessed for all patients who were randomly assigned and received at least one dose of study drug. The primary endpoint was mean absolute change in $LCI_{2.5}$ from baseline at all study visits up to and including week 24. Key secondary endpoints included the average absolute change in sweat chloride concentration from baseline at day 15 and week 4, absolute change in BMI from baseline at week 24, and average absolute change in CFQ-R respiratory domain score from baseline study visit up to and including week 24. Other secondary endpoints included absolute change in $LCI_{5.0}$ (average of all visits up to and including week 24), absolute and relative change in $ppFEV_1$ (average of all visits up to and including week 24), nutritional parameters (weight, height, and corresponding *Z* scores), absolute change in Treatment Satisfaction Questionnaire for Medication domains (average of all visits up to and including week 24), time-to-first pulmonary exacerbation (up to week 24), event of having at least one pulmonary exacerbation (up to week 24), number of pulmonary exacerbations (up to week 24), safety, and pharmacokinetics of lumacaftor (and its metabolite M28-LUM) and ivacaftor (and metabolites M1-IVA and M6-IVA). An independent data monitoring committee safety review was done after 100 patients completed week 4 of treatment.

	Lumacaftor and ivacaftor (n=103)	Placebo (n=101)	Overall (n=204)
Sex			
Female	63 (61%)	58 (57%)	121 (59%)
Male	40 (39%)	43 (43%)	83 (41%)
Age at baseline, years	8·7 (1·6)	8·9 (1·6)	8·8 (1·6)
Geographical distribution			
North America	59 (57%)	60 (59%)	119 (58%)
Europe	28 (27%)	29 (29%)	57 (28%)
Australia	16 (16%)	12 (12%)	28 (14%)
Height, cm	133·2 (10·8)	134·4 (10·3)	133·8 (10·5)
Height-for-age *Z* score	−0·1 (1·0)	−0·2 (0·8)	−0·1 (0·9)
Weight, kg	29·4 (6·5)	30·2 (6·8)	29·8 (6·6)
<25 kg	30 (29%)	28 (28%)	58 (28%)
≥25 kg	73 (71%)	73 (72%)	146 (72%)
Weight-for-age *Z* score	−0·2 (0·8)	−0·2 (0·8)	−0·2 (0·8)
BMI, kg/m²	16·4 (1·7)	16·6 (2·0)	16·5 (1·8)
BMI-for-age *Z* score	−0·1 (0·8)	−0·1 (0·9)	−0·1 (0·9)
$LCI_{2.5}$	10·3 (2·4)	10·3 (2·2)	10·3 (2·3)
Sweat chloride concentration, mmol/L	102·6 (10·3)	103·4 (9·8)	103·0 (10·1)
$ppFEV_1$, percentage points	88·8 (13·7)	90·7 (10·8)	89·8 (12·4)
<70	10 (10%)	1 (1%)	11 (5%)
≥70 to <90	42 (41%)	47 (47%)	89 (44%)
≥90 to ≤105	38 (37%)	44 (44%)	82 (40%)
>105	12 (12%)	9 (9%)	21 (10%)
Patients receiving medications prior to day 1			
Dornase alfa	88 (85%)	88 (87%)	176 (86%)
Any inhaled antibiotic	20 (19%)	30 (30%)	50 (25%)
Any inhaled bronchodilator	85 (83%)	82 (81%)	167 (82%)
Any inhaled hypertonic saline	67 (65%)	54 (53%)	121 (59%)
Any inhaled corticosteroids	38 (37%)	47 (47%)	85 (42%)
Pseudomonas positive	44 (43%)	43 (43%)	87 (43%)

Values are n (%) or mean (SD). BMI=body-mass index. $LCI_{2.5}$=lung clearance index 2·5. $ppFEV_1$=percent predicted forced expiratory volume in 1 second.

Table 1: **Baseline characteristics and demographics**

Statistical analyses

The primary analysis of the primary efficacy endpoint—absolute change from baseline in $LCI_{2.5}$ (including all measurements up to and including week 24, both on-treatment measurements and measurements after treatment discontinuation)—was based on a mixed-effects model for repeated measurements (MMRM; SAS statistical software package, SAS Institute, Cary, NC, USA). The model included absolute change from baseline in $LCI_{2.5}$ as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and patient as a random effect, with adjustment for weight (<25 kg

vs ≥25 kg), $ppFEV_1$ severity (<90 *vs* ≥90), and baseline $LCI_{2.5}$ as a continuous variable.

The primary result obtained from the MMRM model was the treatment effect averaged from each study visit until week 24. The target sample size of 200 patients was mainly driven by population size and feasibility considerations. Power calculations and MMRMs for secondary endpoints are detailed in the appendix. This study was registered with ClinicalTrials.gov, number NCT02514473.

Role of the funding source

Vertex Pharmaceuticals provided funding for this study and for editorial support in manuscript development. Vertex Pharmaceuticals was involved in study design, data collection, analysis, and interpretation, and reviewed and provided feedback on this manuscript. The authors had full editorial control of this manuscript, provided their final approval of all content, and had final decision to submit for publication.

Results

Between July 23, 2015, and Sept 20, 2016, 206 patients were enrolled and randomly assigned to receive lumacaftor and ivacaftor (n=104) or placebo (n=102). 204 patients received at least one dose of study drug (103 lumacaftor and ivacaftor, 101 placebo; figure 1). 97 (94%) of 103 patients in the lumacaftor and ivacaftor group and 96 (95%) of 101 patients in the placebo group completed 24 weeks of treatment. Treatment discontinuation due to adverse events (respiration abnormal; elevated aminotransferases) occurred in three (3%) of 103 patients in the lumacaftor and ivacaftor group and two (2%) of 101 patients in the placebo group. Compliance percentage over 80% with medication (calculated as 100×[total days continuous medication/duration of total exposure]) was high in both groups: 97·9% with lumacaftor and ivacaftor and 99·7% with placebo.

Baseline characteristics were generally similar across the two treatment groups (table 1). Mean baseline $ppFEV_1$ was slightly lower in the lumacaftor and ivacaftor group and approximately one half of patients in the study had $ppFEV_1$ of 90 or more, representing a population with well preserved lung function. In the placebo group, a higher proportion of patients received inhaled antibiotics and inhaled corticosteroids, and a lower proportion received inhaled hypertonic saline prior to study day 1 compared with the lumacaftor and ivacaftor group.

There was a statistically significant within-group average absolute improvement from baseline in $LCI_{2.5}$ up to and including week 24 (least squares mean –1·01, 95% CI –1·27 to –0·75; p<0·0001) among patients treated with lumacaftor and ivacaftor. The change from baseline in the placebo group was not significant (0·08, 95% CI –0·18 to 0·34; p=0·5390). The difference between the lumacaftor and ivacaftor and placebo groups was significant (p<0·0001); these improvements in $LCI_{2.5}$ were apparent by day 15 of active treatment and were sustained throughout the remaining study visits (figure 2).

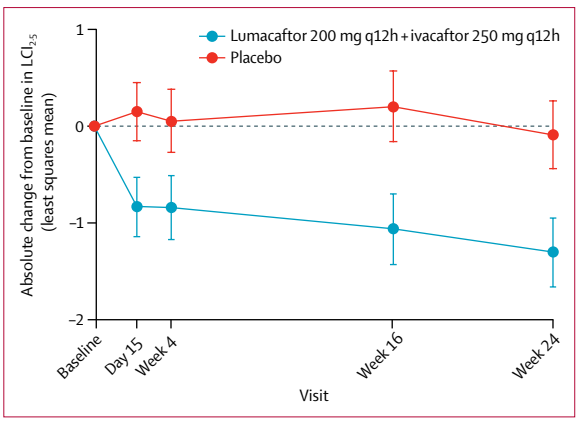

Figure 2: **Absolute change from baseline in $LCI_{2.5}$**
Values shown are adjusted for MMRM covariates. Error bars are 95% CI. Decrease in $LCI_{2.5}$ indicates improvement. $LCI_{2.5}$=lung clearance index. MMRM=mixed-effects model for repeated measures. q12h=every 12 hours.

	Lumacaftor and ivacaftor (n=103*)	Placebo (n=101*)	Treatment difference versus placebo
Absolute change in $LCI_{2.5}$ up to and including week 24	–1·0 (–1·3 to –0·8) p<0·0001	0·1 (–0·2 to 0·3) p=0·5390	–1·1 (–1·4 to –0·8) p<0·0001
Average absolute change in sweat chloride concentration at day 15 and week 4	–20·0 (–22·0, –18·1) p<0·0001	0·8 (–1·2 to 2·8) p=0·4208	–20·8 (–23·4 to –18·2) p<0·0001
Absolute change in BMI at week 24	0·4 (0·3 to 0·5) p<0·0001	0·3 (0·1 to 0·4) p=0·0002	0·1 (–0·1 to 0·3) p=0·2522
Absolute change in BMI-for-age *Z* score at week 24	0·1 (0·0 to 0·2) p=0·0310	0·1 (–0·0 to 0·1) p=0·1739	0·0 (–0·1 to 0·1) p=0·5648
Absolute change in CFQ-R respiratory domain score up to and including week 24	5·5 (3·4 to 7·6) p<0·0001	3·0 (1·0 to 5·0) p=0·0035	2·5 (–0·1 to 5·1) p=0·0628
Absolute change in $ppFEV_1$ up to and including week 24	1·1 (–0·4 to 2·6) p=0·1483	–1·3 (–2·8 to 0·2) p=0·0899	2·4 (0·4 to 4·4) p=0·0182

All endpoints shown are change from baseline. All values are least squares mean (95% CI). *p values are within-group. BMI=body-mass index.CFQ-R=Cystic Fibrosis Questionnaire-Revised. $LCI_{2.5}$=lung clearance index 2·5. $ppFEV_1$=percent predicted forced expiratory volume in 1 second.

Table 2: **Primary and secondary efficacy endpoints**

Average absolute change from baseline in sweat chloride concentration (at day 15 and week 4) was significant in lumacaftor-treated and ivacaftor-treated patients (within-group least squares mean –20·0, 95% CI –22·0 to –18·1; p<0·0001, table 2), as was the treatment difference versus placebo (least squares mean difference –20·8, 95% CI –23·4 to –18·2; p<0·0001). Significant reductions in sweat chloride concentrations versus placebo were observed at day 15 of lumacaftor and ivacaftor treatment and all subsequent visits (figure 3A).

Significant increases in BMI from baseline were observed in both groups at week 24 (figure 3B) and in BMI-for-age *Z* score in the lumacaftor and ivacaftor

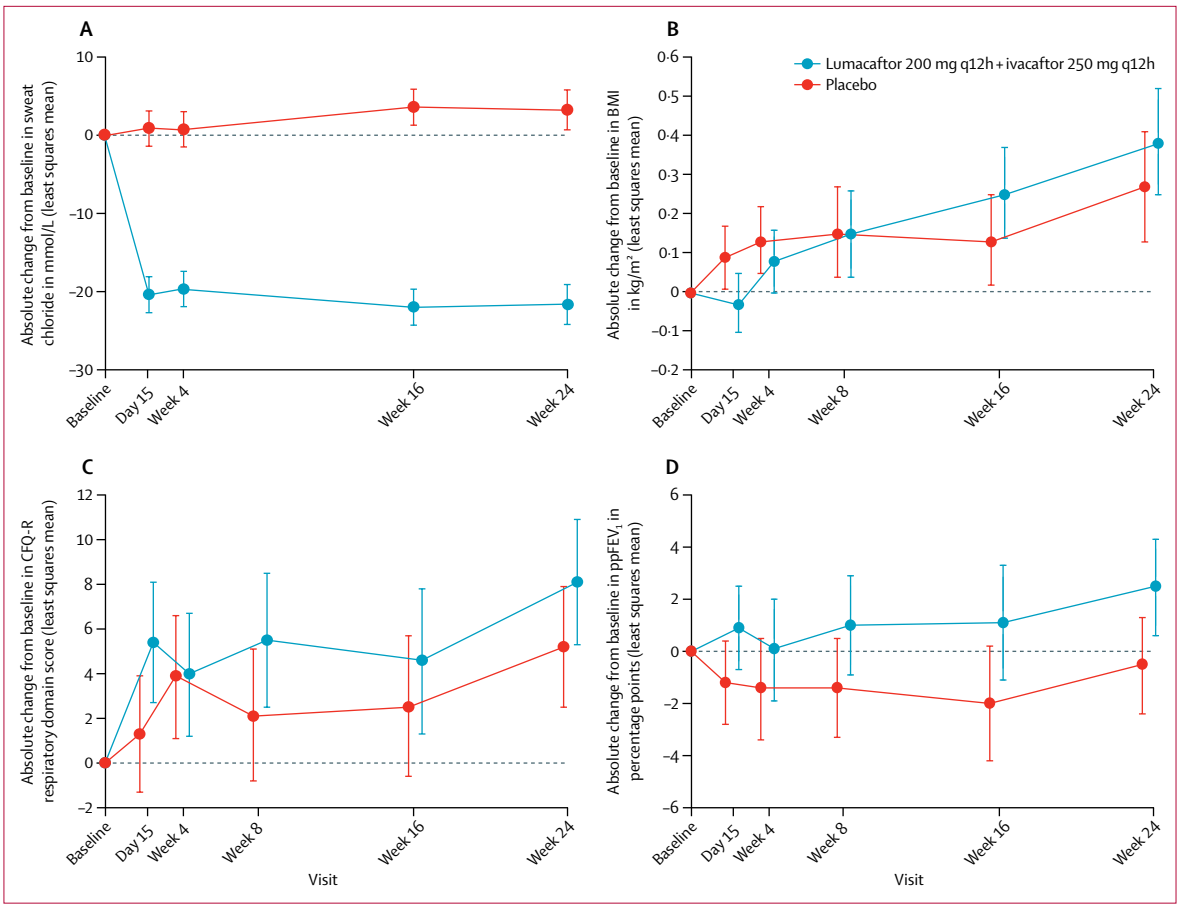

Figure 3: **Absolute change from baseline in secondary efficacy endpoints**
(A) sweat chloride concentration, (B) BMI, (C) CFQ-R respiratory domain score, and (D) $ppFEV_1$. Values are adjusted for MMRM covariates. Decrease in sweat chloride concentration indicates improvement. Error bars are 95% CI. BMI=body-mass index. CFQ-R=Cystic Fibrosis Questionnaire-Revised. MMRM=mixed-effects model for repeated measures. $ppFEV_1$=percent predicted forced expiratory volume in 1 second. q12h=every 12 hours.

group, but treatment differences did not reach significance for either measure (table 2). CFQ-R respiratory domain scores were improved over baseline through week 24 in both groups, and the difference observed between the groups was not significant (table 2, figure 3C).

Absolute change from baseline in $ppFEV_1$ averaged through week 24 was not significant in either treatment group. In the placebo group, within-group $ppFEV_1$ was less than baseline at all visits, but in the lumacaftor and ivacaftor group, mean $ppFEV_1$ did not fall below baseline at any study visit (figure 3D). The between-group difference in absolute change in $ppFEV_1$ averaged through week 24 was significant in favour of lumacaftor and ivacaftor (least squares mean difference *vs* placebo 2·4, 95% CI 0·4–4·4; p=0.0182, table 2).

One patient in the placebo group had FE-1 more than 200 µg/g stool (considered the cutoff for exocrine pancreatic sufficiency) at baseline and week 24, and one patient in the lumacaftor and ivacaftor group had FE-1 more than 200 µg/g stool at week 24 and less than 15 µg/g stool at baseline. All other patients with measurements at baseline and week 24 had FE-1 concentrations less than 200 µg/g stool at both visits. Further details are provided in the appendix.

Adverse events were reported in 196 (96%) of 204 patients; in most patients, these were mild (43%) or moderate (48%) in severity. The proportion of patients reporting adverse events was similar in the treatment and placebo groups (table 3), with cough being the most common adverse event (46 [45%] of 103 in the lumacaftor and ivacaftor group and 47 [47%] of 101 in the placebo group). Productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, rhinorrhea, and sputum increased were observed more frequently in the lumacaftor and ivacaftor treatment group than in the placebo group.

Serious adverse events were reported in 13 (13%) of 103 patients in the lumacaftor and ivacaftor group and were considered related to study drug in two patients (one drug interaction, one obstructive airways disorder). 11 (11%) of 101 patients in the placebo group

reported serious adverse events, which were considered treatment-related in three (one distal intestinal obstruction syndrome, two elevated aminotransferases). There were no deaths during the study period. Respiratory events were reported in 19 (18%) of 103 patients in the lumacaftor and ivacaftor group (six respiration abnormal, five dyspnoea, five wheezing, four asthma) and 13 (13%) of 101 in the placebo group (five dyspnoea, four respiration abnormal, three wheezing, one chest discomfort, one asthma; some patients had more than one respiratory event). Respiratory events occurred within the first week of study treatment in eight patients in the lumacaftor and ivacaftor group and six patients in the placebo group; events resolved within 2 weeks of onset in six of the patients in the treatment group and five of the patients in the placebo group. One (1%) of 103 patients in the lumacaftor and ivacaftor group had a respiratory event (respiration abnormal) that led to interruption (at study day 6) and discontinuation (at study day 9) of treatment. At day 1, a short-term, post-dose $ppFEV_1$ decline was observed in patients receiving lumacaftor and ivacaftor, but this was generally asymptomatic with few concurrent respiratory events (table 4). A markedly smaller decline was observed post-dose at day 15, and no decline was observed by week 16.

Alanine aminotransferase or aspartate aminotransferase elevations more than three times the upper limit of normal were observed in 21 (10%) of 204 patients, with more in the lumacaftor and ivacaftor group (13 [13%] of 103) than in the placebo group (eight [8%] of 101). Eight patients had elevations more than five times the upper limit of normal (five [5%] of 103 patients receiving lumacaftor and ivacaftor, three [3%] of 101 patients receiving placebo), and three patients had elevations more than eight times the upper limit of normal (one [1%] of 103 patients in the lumacaftor and ivacaftor group, two [2%] of 101 patients in the placebo group). All of these elevations were isolated without concomitant elevations in bilirubin.

There were no meaningful changes in vital signs, including blood pressure (appendix), in patients treated with lumacaftor and ivacaftor compared with patients given placebo.

	Lumacaftor and ivacaftor (n=103)	Placebo (n=101)	Overall (n=204)
Patients with any adverse event	98 (95%)	98 (97%)	196 (96%)
Treatment-emergent adverse events with incidence >10% in any treatment group			
Cough	46 (45%)	47 (47%)	93 (46%)
Infective pulmonary exacerbation of cystic fibrosis	20 (19%)	18 (18%)	38 (19%)
Productive cough	18 (17%)	6 (6%)	24 (12%)
Nasal congestion	17 (17%)	8 (8%)	25 (12%)
Oropharyngeal pain	15 (15%)	10 (10%)	25 (12%)
Pyrexia	15 (15%)	20 (20%)	35 (17%)
Upper abdominal pain	13 (13%)	7 (7%)	20 (10%)
Headache	13 (13%)	9 (9%)	22 (11%)
Upper respiratory tract infection	13 (13%)	10 (10%)	23 (11%)
Sputum increased	11 (11%)	2 (2%)	13 (6%)
Abdominal pain	10 (10%)	10 (10%)	20 (10%)
Nausea	10 (10%)	9 (9%)	19 (9%)
Rhinorrhoea	10 (10%)	5 (5%)	15 (7%)
Vomiting	10 (10%)	10 (10%)	20 (10%)
Fatigue	9 (9%)	11 (11%)	20 (10%)

Values are n (%).

Table 3: **Treatment-emergent adverse events**

	Lumacaftor and ivacaftor	Placebo
Day 1		
≤2 hours post dose	−5·5 (8·2) n=91	−0·1 (5·1) n=97
4–6 hours post dose	−7·7 (7·3) n=92	−1·4 (7·1) n=96
24 hours post dose	−4·1 (10·1) n=38	−1·7 (6·8) n=44
Day 15		
≤2 hours post dose	−1·4 (7·0) n=88	0·9 (5·5) n=87
4–6 hours post dose	−1·3 (6·4) n=86	0·1 (5·2) n=87
Week 16		
≤2 hours post dose	1·7 (4·8) n=33	0·8 (5·8) n=42
4–6 hours post dose	0·5 (7·4) n=33	0·6 (7·1) n=42
Week 24		
≤2 hours post dose	0·3 (4·1) n=25	0·0 (3·4) n=23
4–6 hours post dose	−2·8 (4·0) n=24	0·1 (4·3) n=24

Values are mean absolute change in percentage points (SD). $ppFEV_1$=percent predicted forced expiratory volume in 1 second.

Table 4: **Acute change in $ppFEV_1$ following study drug administration**

Discussion

In this placebo-controlled study, combination lumacaftor and ivacaftor treatment decreased $LCI_{2.5}$ and sweat chloride concentrations, maintained spirometric lung function, and was well tolerated in patients aged 6–11 years with cystic fibrosis homozygous for the *F508del-CFTR* mutation.

Patients receiving lumacaftor and ivacaftor had statistically significant improvement in $LCI_{2.5}$ based on the average decrease from baseline across all study visits and a significant treatment effect versus placebo. The magnitude of both the within-group improvement, a reduction of −1·01, and the between-group treatment difference versus placebo, −1·09, observed in this study are similar to findings in the previous open-label study in paediatric patients (−0·86 at day 15, −1·08 at week 4, and −0·88 at week 24).[13] The

improvement observed in this study is also similar in magnitude to the effect described with hypertonic saline[25] and dornase alfa,[26] albeit using a different inert gas to measure $LCI_{2.5}$ (sulfur hexafluoride, as opposed to nitrogen-based multiple-breath washout). It should be noted that patients in this study were permitted to continue receiving their existing medications during the study period, including dornase alfa and hypertonic saline. This suggests that the effect of lumacaftor and ivacaftor on $LCI_{2.5}$ would have occured over and above any improvement caused by hypertonic saline or dornase alfa in patients receiving these drugs. The magnitude of effect on $LCI_{2.5}$ was smaller than that observed in a phase 2 study of ivacaftor, also done in patients aged 6 years or older but with at least one *G551D-CFTR* mutation (–2·07 at 4 weeks);[27] a greater beneficial effect of ivacaftor on spirometry and other efficacy measures was also reported in the phase 2 trial than was observed in this study.

In this and previous studies,[13] children aged 6–11 years with cystic fibrosis generally had well preserved spirometry. Although FEV_1 has been the standard for clinical trial assessments in cystic fibrosis, evidence has suggested that $LCI_{2.5}$ is more sensitive to the presence of early structural lung abnormalities associated with cystic fibrosis, particularly in younger patients.[18,19] $LCI_{2.5}$ is considered a reliable, well validated, and responsive clinical endpoint measure,[28] and treatment effects with hypertonic saline,[25] dornase alfa,[26] ivacaftor,[27] and lumacaftor and ivacaftor[13] have been detected using $LCI_{2.5}$ in paediatric patients with cystic fibrosis. Elevated $LCI_{2.5}$ values reflect increasing unevenness of gas mixing within the lung that is a consequence of early lung disease in cystic fibrosis (eg, secondary to mucus plugging and airway wall changes such as bronchiectasis).[29] To our knowledge, this study represents the first time that $LCI_{2.5}$ has been used as a primary outcome measure in a large multicentre phase 3 trial.

Consistent with known characteristics of patients with cystic fibrosis homozygous for *F508del-CFTR*[30] and with data from our previous phase 3 open-label study in paediatric patients,[13] sweat chloride measurements at baseline were 100 mmol/L or more. We observed a decrease in sweat chloride concentration versus baseline in patients treated with lumacaftor and ivacaftor that was apparent from day 15 and persisted throughout the study; no decrease was observed in patients given placebo. The magnitude, rapid onset, and durability of this effect are all in accordance with findings from our previous paediatric open-label trial[13] and in adult patients with advanced lung disease[31] (sweat chloride concentration was not measured in the TRAFFIC and TRANSPORT trials) and provide further evidence that combination lumacaftor and ivacaftor therapy increases CFTR activity in patients homozygous for *F508del*.

An increase in mean CFQ-R respiratory domain score from baseline was observed in the lumacaftor and ivacaftor group (5·5 points). This increase is consistent with changes observed in the phase 3 open-label study in paediatric patients,[13] and exceeds the minimal clinically important difference in cystic fibrosis populations (4·0 points) determined from analyses of two open-label studies of tobramycin in patients with cystic fibrosis.[32] However, it was not significantly different from that observed in patients who received placebo (3·0 points).

Mean baseline $ppFEV_1$ in the study population was 89·8, and approximately one half of patients had $ppFEV_1$ of 90 or above, representing well preserved spirometric lung function. This is in contrast to the TRAFFIC/TRANSPORT studies, in which mean baseline $ppFEV_1$ was 61, and most patients had measurements less than 70.[12] Significant improvement over baseline was not detected in patients receiving lumacaftor and ivacaftor. However, there was a treatment difference in $ppFEV_1$ compared with placebo patients in this study; $ppFEV_1$ remained stable in the lumacaftor and ivacaftor group but declined in the placebo group. This finding is consistent with the previous observation in older patients that lumacaftor and ivacaftor has a disease-modifying effect on the progressive decline in lung function associated with cystic fibrosis.[33] This conclusion is of particular importance in paediatric patients for whom preservation of lung function is a primary goal in clinical practice.

Nutritional status is an important consideration in young patients, as measures of nutrition in the normal range are associated with better pulmonary function and survival in adults and children with cystic fibrosis.[34] Similar to observations from the open-label paediatric study,[13] patients receiving lumacaftor and ivacaftor showed significant increase in BMI over the course of this study. However, there was no significant treatment effect versus placebo; patients in the placebo group also showed significant improvement in BMI during the study period. Outcomes such as BMI and CFQ-R are well preserved, and we hypothesise that detection of response might be limited by ceiling effects.

Elastase secreted from the pancreas remains intact during its passage through the intestine, and its concentration in faeces (FE-1) provides a reliable diagnostic test for pancreatic function in patients with cystic fibrosis,[35] with concentrations above 200 µg/g stool considered the cutoff for exocrine pancreatic sufficiency. Most patients homozygous for *F508del-CFTR* have FE-1 concentrations less than the capacity of our detection method (15 µg/g stool).[36] In our study, 12 (15%) of 78 patients had detectable concentrations

of FE-1 at week 24 of lumacaftor and ivacaftor treatment, compared with four (5%) of 75 receiving placebo; five (6%) of 78 patients in the lumacaftor and ivacaftor group and four (5%) of 75 patients in the placebo group had detectable concentrations at baseline. 90 patients in the lumacaftor and ivacaftor group were assessed for FE-1, but only 78 had non-missing records at baseline and week 24. Similarly, 92 were assessed in the placebo group, but only 75 had non-missing records at baseline and week 24. Only one patient in each group had FE-1 more than 200 µg/g stool at the end of the study (appendix). Although increased FE-1 has been seen with modulator therapy in other cystic fibrosis genotypes,[37] further exploration of the effect of CFTR modulators on exocrine pancreatic function, particularly for younger patients in whom pancreatic damage is not established, is warranted.

In previous phase 3 studies of lumacaftor and ivacaftor in patients with cystic fibrosis aged at least 12 years homozygous for *F508del-CFTR*, treatment with lumacaftor and ivacaftor was generally safe and well tolerated.[12,33] The most common adverse events were typical for patients with cystic fibrosis. There was an imbalance in early respiratory events; these events were generally mild to moderate in severity and resolved without interrupting treatment. An imbalance in serious adverse events associated with liver function was seen in these previous studies, and increased blood pressure was observed in some patients, although no adverse events related to increased blood pressure were reported. The safety profile for lumacaftor and ivacaftor in our study was generally consistent with these observations, although there were no meaningful changes in blood pressure and onset of respiratory events was less associated with lumacaftor and ivacaftor initiation.

Most adverse events were respiratory or infective and were reported for both lumacaftor and ivacaftor and placebo groups. However, productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, rhinorrhea, and sputum increased were observed more frequently in the lumacaftor and ivacaftor treatment group than in the placebo group. Of 204 patients, two treated with lumacaftor and ivacaftor and three receiving placebo had serious adverse events that were considered to be related to study treatment. The incidence of respiratory events was 18% in patients receiving lumacaftor and ivacaftor in this study, versus 13% in patients receiving placebo, and onset was not associated with treatment initiation to the same extent as was observed in TRAFFIC, TRANSPORT, and the open-label extension of these two trials (PROGRESS).[12,33]

Initiation of lumacaftor and ivacaftor combination therapy in the study population was well tolerated, and although a post-dose decline in $ppFEV_1$ was observed during the first week following initiation, this resolved with continuing treatment.

The rate of abnormal aminotransferase values in this study population was similar to that seen in patients of the same age group in the previous open-label study in patients with cystic fibrosis homozygous for *F508del-CFTR*,[13] but higher than that observed in older patients.[12] Alanine aminotransferase or aspartate aminotransferase elevations more than 3 times the upper limit of normal were observed in 13% of patients from the lumacaftor and ivacaftor group in this study compared with 5% of the patients treated with lumacaftor and ivacaftor in the TRAFFIC/TRANSPORT trials[12]; 8% of patients in the placebo group in our study showed elevations above 3 times the upper limit of normal. Overall, the higher rate of aminotransferase elevations in younger patients was generally consistent with expected outcomes in paediatric patients with cystic fibrosis who are known to have a high background rate of aminotransferase abnormalities.[38]

Our trial is limited by the highly controlled and monitored context common to all clinical studies. In addition, our trial employed the multiple-breath washout measurement, $LCI_{2.5}$, as the primary endpoint. To our knowledge, $LCI_{2.5}$ has not been previously used as the primary endpoint in a large multicentre clinical trial.

In conclusion, this study has shown that lumacaftor and ivacaftor improved $LCI_{2.5}$, a sensitive measure of early cystic fibrosis-related lung disease and ventilatory distribution abnormalities, compared with placebo in paediatric patients with cystic fibrosis homozygous for *F508del-CFTR*. Sweat chloride concentration was also significantly improved (decreased) versus placebo, lending mechanistic validation to the pulmonary findings as it represents an improvement in CFTR function in response to modulator therapy. Although $ppFEV_1$ did not change significantly from baseline in either group, there was a significant treatment effect reflecting preservation of lung function with lumacaftor and ivacaftor and functional decline, even in the relatively short period of 24 weeks, with placebo. Taken together, these findings support the need for early initiation of treatment. The safety profile of lumacaftor and ivacaftor was generally consistent with that observed in previous phase 3 studies.

Contributors

The study sponsor (Vertex Pharmaceuticals Incorporated) designed the protocol in collaboration with the academic authors. Site investigators collected the data, which were analysed by the sponsor. PDR, SS, and JCD helped coordinate or deliver training, certification, and central over-reading services for multiple-breath washout measurements done during the study. All authors had full access to the study data. FR, GM, and ST guided the initial drafting of the manuscript, with input from all other authors. All authors participated in subsequent revisions and the decision to submit the manuscript for publication.

Declaration of interests
FR acts as a consultant for, and has received an investigator-initiated grant from Vertex Pharmaceuticals Incorporated. CH, GM, ST, XH, and DW are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. FR's and SS's institution received reimbursement from Vertex Pharmaceuticals Incorporated for provision of multiple-breath washout quality over-reading services. CEM has received clinical trial funding from Vertex Pharmaceuticals Incorporated, Parion Sciences Incorporated, Proteostasis Therapeutics, and Gilead Sciences Incorporated, research funding from the US Cystic Fibrosis Foundation, Cystic Fibrosis Research Incorporated, and the National Institutes of Health, and consulting and advising honoraria from Gilead Sciences Incorporated and Concert Pharmaceuticals Incorporated. PDR's institution was reimbursed by Vertex Pharmaceuticals Incorporated for the provision of multiple-breath washout operator training and certification and quality over-reading services. JCD has served on advisory boards for Novartis, Pharmaxis, Proteostasis Therapeutics, Pulmocide, and Vertex Pharmaceuticals Incorporated, has undertaken educational activities for Vertex Pharmaceuticals Incorporated (the sponsor of the study), for which her institution, Imperial College, has received payment, and has received funding from the ECFS in support of a core LCI facility on behalf of Clinical Trials Network sites.

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