Lumacaftor/Ivacaftor in Patients Aged 6–11 Years with Cystic Fibrosis and Homozygous for *F508del-CFTR*

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Abstract

Rationale: Combination lumacaftor/ivacaftor has been shown to improve lung function and other endpoints in patients aged 12 years and older with cystic fibrosis and homozygous for *F508del-CFTR*, but it has not been assessed in younger patients.

Objectives: In this open-label phase III trial, we evaluated the safety, tolerability, pharmacodynamics, and efficacy of lumacaftor/ivacaftor combination therapy in patients aged 6–11 years with cystic fibrosis who were homozygous for *F508del-CFTR*.

Methods: Patients (N = 58) received 200 mg lumacaftor/250 mg ivacaftor orally every 12 hours for 24 weeks in addition to their existing cystic fibrosis medications.

Measurements and Main Results: Lumacaftor/ivacaftor was well tolerated; the safety profile was generally similar to that observed in larger lumacaftor/ivacaftor trials with older patients. Four patients discontinued (two because of drug-related adverse events: elevated liver transaminases, n = 1; rash, n = 1). No safety concerns were associated with spirometry. No significant changes in percent predicted FEV_1 were observed (change from baseline at Week 24, +2.5 percentage points; 95% confidence interval [CI], −0.2 to 5.2; $P = 0.0671$). At Week 24, significant improvements from baseline were observed in sweat chloride (−24.8 mmol/L; 95% CI, −29.1 to −20.5; $P < 0.0001$), body mass index *z* score (+0.15; 95% CI, 0.08 to 0.22; $P < 0.0001$), Cystic Fibrosis Questionnaire-Revised respiratory domain score (+5.4; 95% CI, 1.4 to 9.4; $P = 0.0085$), and lung clearance index based on lung volume turnover required to reach 2.5% of starting N_2 concentration (−0.88; 95% CI, −1.40 to −0.37; $P = 0.0018$).

Conclusions: Lumacaftor/ivacaftor was well tolerated in this young population; no new safety concerns were identified. Improvements in lung clearance index, sweat chloride, nutritional status, and health-related quality of life were observed after 24 weeks of treatment.

Clinical trial registered with www.clinicaltrials.gov (NCT01897233).

Keywords: cystic fibrosis transmembrane conductance regulator protein; sweat test; lung clearance index; lumacaftor; ivacaftor

Cystic fibrosis (CF) is a progressive genetic disease that affects more than 70,000 children and adults worldwide (1–4). CF affects multiple organ systems and is characterized by loss of lung function consequent to chronic respiratory infections and pulmonary exacerbations, as well as malnutrition associated with exocrine pancreatic insufficiency and digestive dysfunction. Lung disease progression begins in infancy (5), and mortality is primarily associated with respiratory failure due to progressive lung disease (6).

CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an anion channel located in epithelial membranes, as a

(Received in original form August 31, 2016; accepted in final form October 26, 2016)

*A complete list of members may be found in the online supplement.

This study was funded by Vertex Pharmaceuticals Incorporated.

Author Contributions: C.E.M.: guided the initial drafting of the manuscript, with input from all other authors. The study sponsor (Vertex Pharmaceuticals Incorporated) designed the protocol in collaboration with the academic authors. Site investigators collected the data, which were analyzed by the sponsor. All authors had full access to the study data. All authors participated in subsequent revisions and the decision to submit the manuscript for publication.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 195, Iss 7, pp 912–920, Apr 1, 2017

Originally Published in Press as DOI: 10.1164/rccm.201608-1754OC on November 2, 2016
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: In two phase III clinical trials, combination therapy with the cystic fibrosis transmembrane conductance regulator modulators lumacaftor and ivacaftor improved lung function and other endpoints in patients aged 12 years and older with cystic fibrosis (CF) who were homozygous for the *F508del-CFTR* mutation. The safety and efficacy of this combination therapy have not been evaluated in younger patients.

What This Study Adds to the Field: In this open-label phase III study of lumacaftor/ivacaftor in patients with CF aged 6–11 years who were homozygous for the *F508del-CFTR* mutation, the combination therapy was well tolerated over 24 weeks of treatment, with a safety profile similar to that observed in older patients. Sweat chloride rapidly improved after treatment initiation and returned to baseline once therapy was discontinued. Though significant improvements in percent predicted FEV_1 were not observed in this young population with relatively preserved spirometric measures of lung function, the lung clearance index, a lung function measure sensitive to early CF lung disease, did improve significantly, as did body mass index *z* score and quality-of-life measures. These results provide evidence for the safety of lumacaftor/ivacaftor in a younger age group.

consequence of mutations in the *CFTR* gene. The most common *CFTR* mutation is *F508del*, which primarily causes a processing defect that leads to reduced delivery of CFTR protein to epithelial membranes as well as reduced stability and channel opening in the small number of channels that do reach the cell surface (7–9). More than 38% of patients with CF are homozygous for this allele (1).

Correction of the *F508del* processing defect and increased epithelial delivery of CFTR protein have been achieved *in vitro* using the small-molecule CFTR corrector lumacaftor (10). Ivacaftor is a CFTR potentiator that increases the open probability of the CFTR *in vitro* and improves clinical outcomes in patients with CF who have mutations that result in defective channel gating (11–16). Although ivacaftor alone has no clinical effect in *F508del-CFTR* homozygous patients (17), it increases channel open probability in *F508del*-mutant CFTRs that undergo epithelial delivery *in vitro* and has an additive effect with lumacaftor on chloride transport (18). In two randomized, double-blind, placebo-controlled phase III trials, lumacaftor/ivacaftor combination therapy was well tolerated by patients aged 12 years and older with CF who were homozygous for the *F508del-CFTR* mutation and led to improved lung function and body mass index (BMI) and reduced incidence of pulmonary exacerbations (19).

In the present study, we sought to evaluate lumacaftor/ivacaftor combination therapy in younger patients homozygous for this mutation. The safety and pharmacokinetics of multiple doses of lumacaftor/ivacaftor over 14 days in patients aged 6–11 years with CF who were homozygous for the *F508del-CFTR* mutation were assessed in part A of this open-label phase III study, the results of which have been presented previously in abstract form (20). In this article, we present findings from part B of this study, whose primary objective was to evaluate the safety and tolerability of lumacaftor/ivacaftor combination therapy over 24 weeks in this patient population. Efficacy endpoints, including sweat chloride, nutritional status, and quality-of-life measures, were evaluated as a secondary objective.

Methods

Study Oversight

The study protocol was reviewed and approved by an institutional review board at each participating site before initiation of the study. Patient caregivers provided written consent, and, where applicable, patients provided written assent.

Study Participants

Patients were eligible for inclusion if they were 6–11 years of age at screening, had a confirmed diagnosis of CF (21), were homozygous for the *F508del-CFTR* mutation, had a percent predicted FEV_1 greater than or equal to 40 (22), and had stable CF disease as deemed by the investigator at the screening visit. Patients with abnormalities in hemoglobin levels, liver function, or renal function were excluded. All enrolled patients were assigned to receive lumacaftor at a dose of 200 mg and ivacaftor at a dose of 250 mg every 12 hours for 24 weeks. This dosage regimen was selected on the basis of safety, tolerability, and pharmacokinetic data from part A of this study (20). Physicians recommended patients maintain their prestudy medications per the study protocol. Further information regarding eligibility is provided in the online supplement.

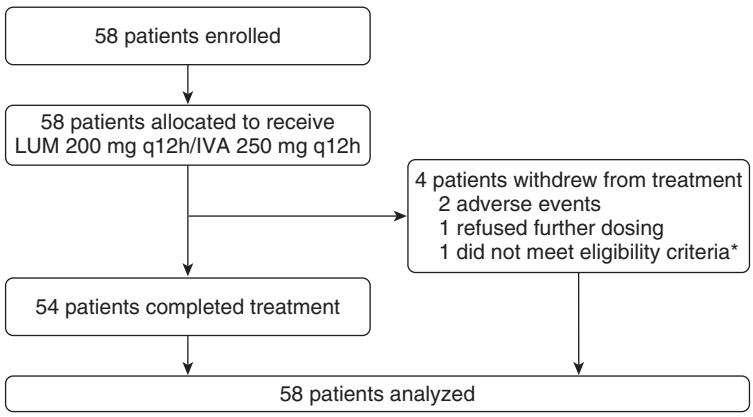

Figure 1. Patient disposition and trial profile. *One subject not homozygous for *F508del-CFTR* was enrolled; this subject was discontinued from treatment after Day 18 and then from the study. IVA = ivacaftor; LUM = lumacaftor; q12h = every 12 h.

Endpoints

The primary objective of this study was to evaluate the safety of lumacaftor/ivacaftor combination therapy as assessed by treatment-emergent adverse events, clinical laboratory values, 12-lead electrocardiograms, vital signs, pulse oximetry, ophthalmologic examinations, and spirometry (including percent predicted FEV_1). Safety parameters were evaluated at screening, follow-up visits during the 24-week treatment period, and 2 weeks after the end of treatment at Week 26. Secondary endpoints included average absolute changes from baseline in sweat chloride at Day 15 and Week 4; absolute change from baseline in BMI, weight, height, and respective *z* scores (*see* online supplement for description of *z*-score calculations) at Week 24 (23); absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score (24) at Week 24; and absolute change in sweat chloride from Week 24 to Week 26. Lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration [$LCI_{2.5}$]) (25) was assessed as an exploratory endpoint in a subset of patients attending centers with expertise in the methodology. Further information about study assessments is available in the online supplement.

Statistical Analyses

The target enrollment of 56 patients was determined on the basis of power calculations for the primary safety endpoint of adverse event incidence, details of which are available in the online supplement. Data were summarized descriptively using mean, SD, SEM, and 95% confidence interval (CI) data. Absolute changes from baseline were evaluated using mixed-effects models for repeated measures, as detailed in the online supplement. Comparisons between Week 24 on-treatment visits and Week 26 safety follow-up visits for percent predicted FEV_1 and sweat chloride were performed using linear regression models, as detailed in the online supplement. A P value less than 0.05 was considered statistically significant. Analyses were conducted using the SAS statistical software package (SAS Institute, Cary, NC).

Results

Participants

A total of 58 patients were enrolled in this study, of whom 54 completed 24 weeks of treatment with lumacaftor/ivacaftor. Two patients discontinued treatment because of adverse events (see Safety subsection below), one withdrew, and one did not meet eligibility criteria (Figure 1). Baseline demographics and clinical characteristics of the enrolled patients are shown in Table 1. The study population was well balanced for

Table 1. Baseline Patient Demographics and Characteristics

Characteristic	Overall (*N* = 58)
Female, n (%)	31 (53.4)
Age, yr, mean (SD)	9.1 (1.53)
Sweat chloride, mmol/L, mean (SD)	105.9 (10.2)
Weight, kg, mean (SD)	31.5 (6.1)
Weight-for-age *z* score, mean (SD)	−0.03 (1.03)
Height, cm, mean (SD)	136.2 (8.6)
Height-for-age *z* score, mean (SD)	0.03 (1.08)
BMI, kg/m^2, mean (SD)	16.89 (1.93)
BMI-for-age *z* score, mean (SD)	0.01 (0.90)
Percent predicted FEV_1 at baseline, mean (SD)	91.4 (13.7)
Patients receiving medications at baseline*, n (%)	
Dornase alfa	50 (86.2)
Any inhaled antibiotic	14 (24.1)
Any bronchodilator	57 (98.3)
Any inhaled bronchodilator	57 (98.3)
Any inhaled hypertonic saline	44 (75.9)
Any inhaled corticosteroids	25 (43.1)
Positive for *Pseudomonas aeruginosa*, n (%)	25 (43.1)

Definition of abbreviation: BMI = body mass index.
*Includes medications received before the first dose of lumacaftor/ivacaftor. The medications may or may not have been continuing at the time the first dose was administered.

Table 2. Adverse Events

Event	Patients [*n* (%)] (*N* = 58)
Any adverse event reported	55 (94.8)
Any serious adverse event reported	4 (6.9)
Interruption of treatment due to an adverse event	6 (10.3)
Discontinuation of treatment due to an adverse event	2 (3.4)
Adverse events by severity	
Mild	22 (37.9)
Moderate	29 (50.0)
Severe	4 (6.9)
Common adverse events (incidence ⩾10%)	
Cough	29 (50.0)
Nasal congestion	12 (20.7)
Infective pulmonary exacerbation	12 (20.7)
Headache	12 (20.7)
Increased sputum	8 (13.8)
Upper abdominal pain	8 (13.8)
Elevated alanine aminotransferase levels	7 (12.1)
Abdominal pain	6 (10.3)
Nausea	6 (10.3)
Vomiting	6 (10.3)
Fatigue	6 (10.3)
Pyrexia	6 (10.3)
Serious adverse events	
Infective pulmonary exacerbation	2 (3.4)
Ileus	1 (1.7)
Elevated liver transaminase levels	1 (1.7)
Respiratory events	4 (6.9)
Dyspnea	1 (1.7)
Respiration abnormal	1 (1.7)
Wheezing	2 (3.4)

Table 3. Proportion of Patients with Liver Function Test Elevations

Parameter	Patients [*n* (%)] (*N* = 57)*
ALT or AST	
>3× ULN	11 (19.3)
>5× ULN	5 (8.8)
>8× ULN	3 (5.3)
Alkaline phosphatase	
>1.5× ULN	1 (1.8)
Total bilirubin	
>1.5× ULN	0

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal. Patients with multiple events were counted once in the worst applicable cutoff category.
*Number of subjects with at least one nonmissing measurement during the period from initiation of study drug to 28 days following last dose.

sex and had generally well-preserved lung function (mean percent predicted FEV_1 [SD], 91.4 [13.7]) and nutritional status (mean BMI-for-age *z* score [SD], 0.01 [0.90]). Thirty patients were enrolled in, and 27 completed, the $LCI_{2.5}$ substudy. Mean baseline $LCI_{2.5}$ (SD) was 9.99 (2.67), which is substantially higher than the mean (SD) of 7.2 (0.5) reported in healthy children (26). Baseline demographics and clinical characteristics of this group are shown in Table E1 in the online supplement.

Safety

Adverse events were reported in 94.8% of patients (Table 2). Two patients discontinued treatment with study drug because of adverse events: one patient because of elevated liver transaminases and one because of rash. In both of these patients, the adverse events were considered related to the study drug and resolved following discontinuation of study drug. No deaths were reported. The most commonly reported adverse events were cough, nasal congestion, infective pulmonary exacerbation, and headache. The majority of patients experienced adverse events of mild or moderate severity. Four patients (6.9%) experienced severe adverse events (ileus, n = 1; sunburn, n = 1; viral gastroenteritis, n = 1; headache, n = 1), none of which were considered related to study drug. Four patients (6.9%) experienced serious adverse events (infective pulmonary exacerbation, n = 2; ileus, n = 1, elevated liver transaminases, n = 1). Study drug was temporarily interrupted for two of the serious adverse events (ileus, 2 d; elevated liver transaminases, 26 d) until they resolved. One patient developed cataracts of mild severity by Week 24 of the study.

Predefined respiratory adverse events of special interest were reported in four patients (dyspnea, n = 1; abnormal respiration, n = 1; wheezing, n = 2). These events were all nonserious and mild in severity, and in three patients they resolved without interruption of study drug. Wheezing was not resolved in one patient but was not considered related to study drug, and study drug was not interrupted. Onset of respiratory events was after Week 4, except for the patient with abnormal respiration (onset Day 1, resolved after 1 d).

Liver function testing was performed at Days 1 and 15 and every 4 weeks starting from Week 4. Elevated liver enzymes considered clinically significant were reported as adverse events. A total of 11 patients (19.3%) had alanine aminotransferase or aspartate aminotransferase elevations greater than three times the upper limit of normal (ULN) at any time during the study period, 5 (8.8%) had alanine aminotransferase or aspartate aminotransferase elevations greater than five times the ULN, 3 (5.3%) had alanine aminotransferase or aspartate aminotransferase elevations greater than eight times the ULN, and no patients had elevated bilirubin; patients with multiple elevation events were counted once per enzyme. Table 3 shows the proportion of patients with liver function test elevations during the study period by elevation category. Study drug treatment was interrupted for two patients because of elevated transaminases, and for a third patient, treatment was interrupted because of elevated transaminases, resumed following recovery, and then permanently discontinued after subsequent transaminase elevation.

A mean increase from baseline in systolic blood pressure was observed at Week 24 of the study (3.0 mm Hg; SE, 1.4), and mean diastolic blood pressure was also increased from baseline at Week 24 (0.8 mm Hg; SE, 1.1). No adverse events associated with increased blood pressure were reported.

Summary data for percent predicted FEV_1 measures are shown in Figure 2. No safety concerns associated with these measures were observed. There were no significant changes detected in percent predicted FEV_1 (Table 4) during the treatment period. Summary data for other spirometric measures are shown in Table E2. A significant drop in percent predicted FEV_1 was observed between the final on-treatment visit at Week 24 and the Week 26 follow-up visit (least squares [LS] mean change, −3.2 percentage points; 95% CI, −4.8 to −1.6; $P = 0.0003$).

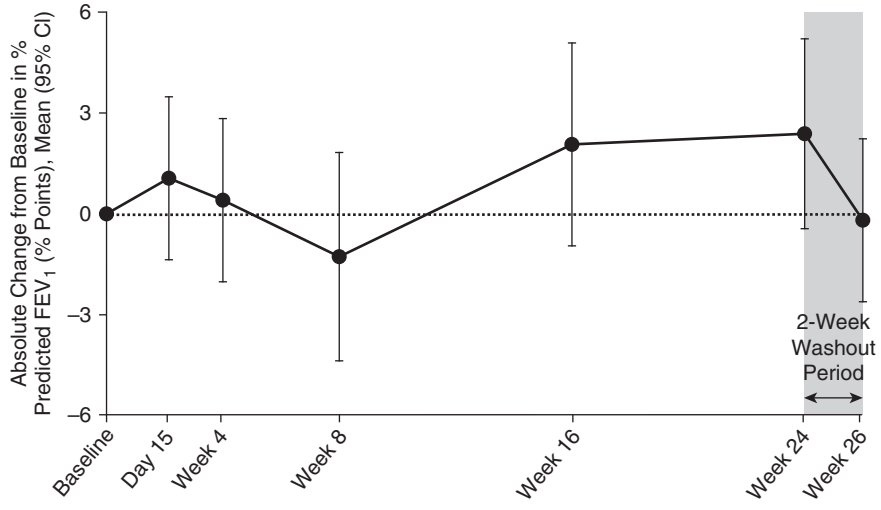

Figure 2. Absolute change from baseline in percent predicted FEV_1. Raw summary statistics (unadjusted for mixed-effects models for repeated measures covariates) are shown for absolute change from baseline at study visits and Week 26 follow-up visit. CI = confidence interval.

Table 4. Absolute Changes from Baseline at Study Visits in Percent Predicted FEV_1 and Efficacy Measures

	Baseline Mean (SD)	Absolute Change from Baseline, LS Mean (95% CI)				
		Day 15	Week 4	Week 8	Week 16	Week 24
Percent predicted FEV_1	91.4 (13.7)	1.1 (−1.1 to 3.3) $P = 0.3281$	0.9 (−1.6 to 3.5) $P = 0.4650$	−1.2 (−4.1 to 1.8) $P = 0.4278$	1.4 (−1.7 to 4.6) $P = 0.3651$	2.5 (−0.2 to 5.2) $P = 0.0671$
Sweat chloride, mmol/L	105.9 (10.2)	−20.4 (−23.9 to −16.9) $P < 0.0001$	−19.0 (−22.9 to −15.2) $P < 0.0001$	NR	NR	−24.8 (−29.1 to −20.5) $P < 0.0001$
BMI, kg/m^2	16.89 (1.93)	0.09 (0.00 to 0.17) $P = 0.0578$	0.12 (0.02 to 0.23) $P = 0.0197$	0.25 (0.11 to 0.40) $P = 0.0008$	0.40 (0.23 to 0.57) $P < 0.0001$	0.64 (0.46 to 0.83) $P < 0.0001$
BMI *z* score	0.01 (0.90)	0.04 (−0.01 to 0.09) $P = 0.1460$	0.07 (0.01 to 0.12) $P = 0.0151$	0.08 (0.01 to 0.15) $P = 0.0205$	0.11 (0.04 to 0.19) $P = 0.0043$	0.15 (0.08 to 0.22) $P < 0.0001$
CFQ-R respiratory domain score	78.3 (14.9)	0.3 (−4.0 to 4.7) $P = 0.8743$	1.3 (−3.9 to 6.5) $P = 0.6242$	6.9 (3.1 to 10.7) $P = 0.0006$	7.3 (4.2 to 10.4) $P < 0.0001$	5.4 (1.4 to 9.4) $P = 0.0085$
$LCI_{2.5}$ (exploratory endpoint in subgroup [n = 30])	9.99 (2.67)	−0.86 (−1.30 to −0.42) $P = 0.0007$	−1.08 (−1.64 to −0.53) $P = 0.0006$	NR	NR	−0.88 (−1.40 to −0.37) $P = 0.0018$

Definition of abbreviations: BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; $LCI_{2.5}$ = lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration); LS = least squares; NR = not recorded.
Absolute changes from baseline were evaluated using mixed-effects models for repeated measures.

Pharmacodynamic and Efficacy Endpoints

Summary data for sweat chloride tests are shown in Figure 3. A substantial and significant average decrease from baseline in sweat chloride concentration was observed at Day 15 and Week 4 (average from both time points, LS mean change, −19.7 mmol/L; 95% CI, −23.2 to −16.3; $P < 0.0001$). Significant decreases were also observed at Week 24 (LS mean change, −24.8 mmol/L; 95% CI, −29.1 to −20.5; $P < 0.0001$) and the other study visits at which sweat chloride was measured (Table 4). At Week 24, 41 of 51 patients with measurements showed a decrease from baseline greater than 15 mmol/L (Figure E1). The LS mean absolute change from Week 24 to the Week 26 follow-up visit was 21.3 mmol/L (95% CI, 18.6 to 24.0; $P < 0.0001$), representing a return to baseline in this measure 2 weeks after ending lumacaftor/ivacaftor therapy.

Summary data for recorded BMI and BMI-for-age *z* scores are shown in Figures 4A and 4B. Significant increases in BMI from baseline were observed at Week 4 (LS mean change, 0.12 kg/m^2; 95% CI, 0.02 to 0.23; $P = 0.0197$) and subsequent study visits (Table 4). We also observed significant increases from baseline in BMI *z* scores at the same visits (Table 4). At the Week 26 follow-up visit, BMI and BMI *z* scores remained above baseline (Figures 4A and 4B). Significant increases from baseline were also observed at treatment visits from Day 15 onward for weight and from Week 4 onward for weight *z* score and height (*see* Table E3). Increased height, weight, and weight *z* scores were maintained at the Week 26 follow-up visit. No significant increases from baseline in height *z* scores were observed at any study visit.

Summary data for respiratory domain scores of the patient-completed CFQ-R are shown in Figure 5. Significant improvements from baseline in mean CFQ-R respiratory domain scores were observed at Week 24 (LS mean change, 5.4; 95% CI, 1.4 to 9.4; $P = 0.0085$), as well as at Week 8 (LS mean, 6.9; 95% CI, 3.1 to 10.7; $P = 0.0006$) and Week 16 (LS mean change, 7.3; 95% CI, 4.2 to 10.4; $P < 0.0001$) (Table 4).

Summary $LCI_{2.5}$ data for patients enrolled in the LCI substudy (n = 30) are shown in Figure 6. A significant decrease (improvement) from baseline in $LCI_{2.5}$ was observed at the Day 15 visit (LS mean change, −0.86; 95% CI, −1.30 to −0.42; $P = 0.0007$) and was sustained at subsequent study visits at Week 4 (LS mean change, −1.08; 95% CI, −1.64 to −0.53; $P < 0.0006$) and Week 24 (LS mean change, −0.88; 95% CI, −1.40 to −0.37; $P = 0.0018$) (Table 4). $LCI_{2.5}$ at the Week 26 follow-up visit remained below baseline (Figure 6).

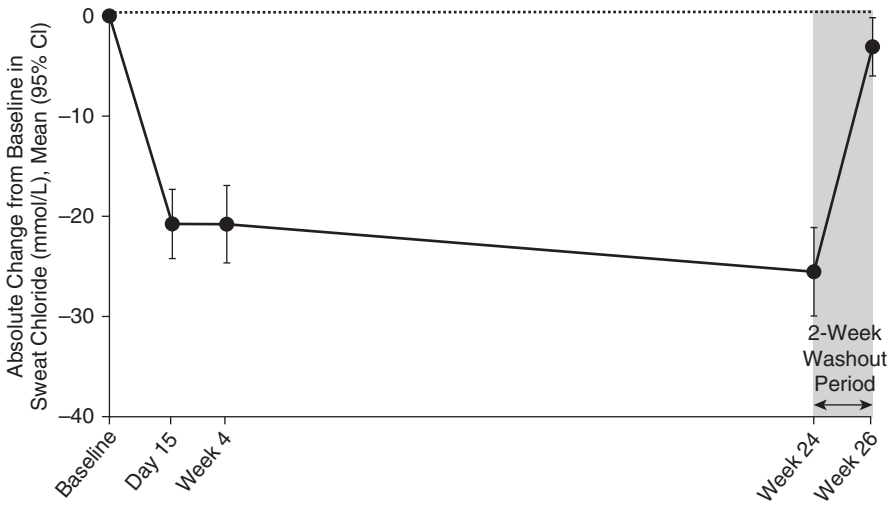

Figure 3. Absolute change from baseline in sweat chloride. Raw summary statistics (unadjusted for mixed-effects models for repeated measures covariates) are shown for absolute change from baseline at study visits and Week 26 follow-up visit. Decrease in sweat chloride indicates improvement. CI = confidence interval.

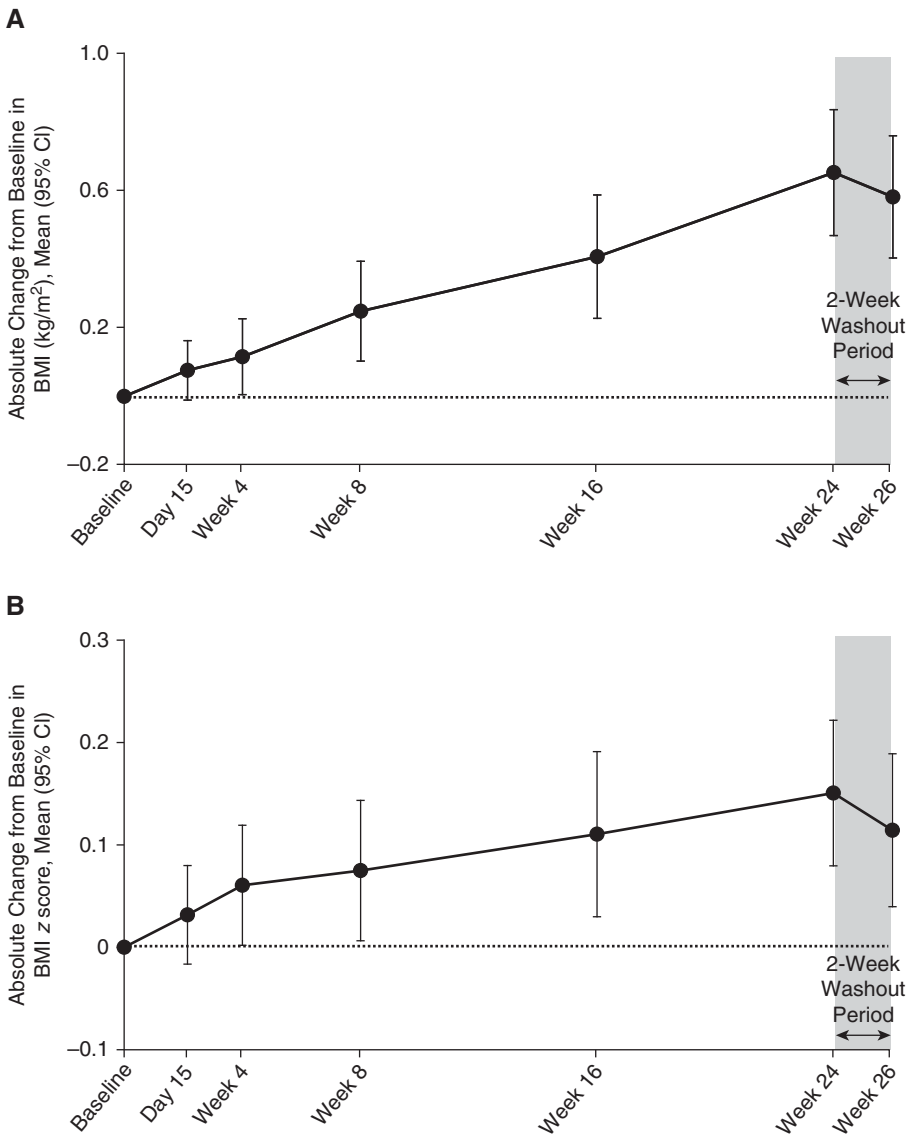

Figure 4. Absolute change from baseline in (*A*) BMI and (*B*) BMI *z* scores. Raw summary statistics (unadjusted for mixed-effects models for repeated measures covariates) are shown for absolute change from baseline at study visits and Week 26 follow-up visit. BMI = body mass index; CI = confidence interval.

Discussion

Combination therapy with lumacaftor, a CFTR corrector, and ivacaftor, a CFTR potentiator, was well tolerated in patients with CF aged 6–11 years who were homozygous for the *F508del-CFTR* mutation, and improvements were demonstrated in sweat chloride; measures of nutritional status; the respiratory domain of the CFQ-R; and $LCI_{2.5}$, a sensitive measure of early CF lung disease.

While an open-label study has limitations in accurately quantifying the frequency of drug-related adverse events, the safety profile was similar to that seen in the TRAFFIC and TRANSPORT studies of lumacaftor/ivacaftor in patients aged 12 years or older (19). Increases in blood pressure observed in the present study were consistent with those reported in TRAFFIC and TRANSPORT, and there were no associated adverse events. The rate of abnormal liver function tests was higher in patients in the present study than in older patients in TRAFFIC and TRANSPORT, but it was generally consistent with elevations seen in placebo-treated patients from the same age group in previous ivacaftor monotherapy trials (12). In TRAFFIC and TRANSPORT, respiratory adverse events occurred mainly at the initiation of lumacaftor/ivacaftor therapy and, in some cases, necessitated interruption or discontinuation of treatment (19). In the present study, respiratory events were observed less frequently; were not associated with drug interruption or discontinuation; and, with one exception, time of onset was more than 28 days after treatment initiation. Respiratory events were all mild in severity and resolved before the end of the study with continued lumacaftor/ivacaftor therapy, except for one patient in whom wheezing (judged not related to study drug) continued throughout the study. Two patients experienced adverse events that required drug discontinuation (rash and elevated liver transaminases), and these events resolved after drug discontinuation.

Baseline lung function in TRAFFIC and TRANSPORT patients was lower than for patients in the present study (mean percent predicted FEV_1 ranged from 60.4 to 60.8 for different treatment arms in TRAFFIC and TRANSPORT vs. 91.4 in the present study) (19), an expected finding, given the progressive nature of airway disease with age in CF (27). Our study was not powered to detect significant changes in spirometric measures, because these changes were planned as safety endpoints. Further, there is limited ability to improve percent predicted FEV_1 in patients with well-preserved lung function. The smaller sample size and milder lung disease in the present study population may explain the lack of a significant effect of study drug on percent predicted FEV_1.

Baseline sweat chloride levels in this study population were high (mean, 105.9 mmol/L), typical for *F508del-CFTR* homozygotes (28). We saw a rapid decrease in sweat chloride after initiation of lumacaftor/ivacaftor therapy in the study population, which persisted while treatment was maintained, indicating that combination therapy increased CFTR activity in these patients. This finding is further supported by the rapid and near-complete reversion to baseline sweat chloride levels after the 2-week post-treatment washout period. Although almost all individual patients showed improvements in sweat chloride in the present study, these improvements were

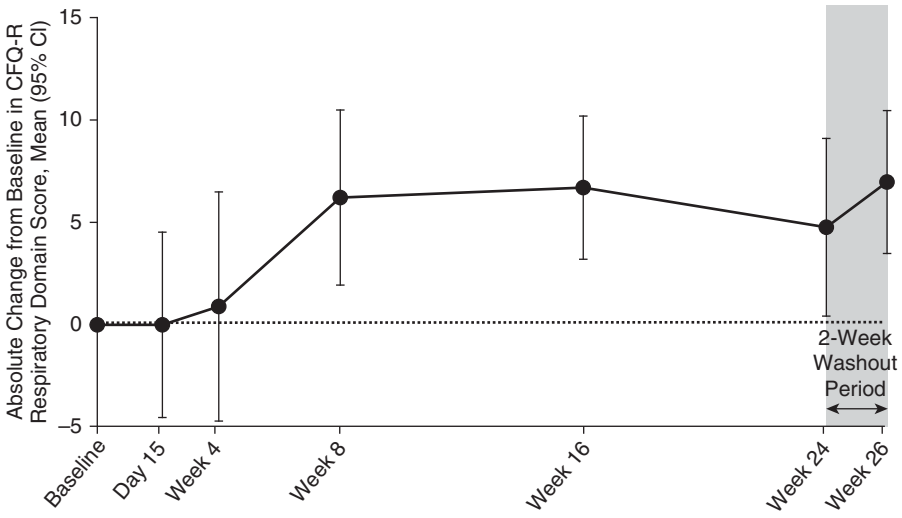

Figure 5. Absolute change from baseline in CFQ-R respiratory domain scores. Raw summary statistics (unadjusted for mixed-effects models for repeated measures covariates) are shown for absolute change from baseline at study visits and Week 26 follow-up visit. Increase in CFQ-R score indicates improvement. CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval.

not as robust as those seen in similarly aged patients with the gating mutation *G551D* who received ivacaftor (>50 mmol/L) (12). This finding was to be expected, given that the *F508del*-mutant CFTR channels have reduced membrane delivery in addition to gating deficits, and is in line with *in vitro* findings, suggesting that lumacaftor only partially rescues the processing defect in *F508del*-mutant CFTR proteins (10).

We observed significant improvement in nutritional parameters over the course of 24 weeks of lumacaftor/ivacaftor therapy. Though mean BMI-for-age *z* score at baseline was in the normal range for our study population, it improved during treatment, beginning as early as 4 weeks following the initiation of lumacaftor/ivacaftor therapy. Maintaining and improving nutritional status is an important consideration in CF because patients in the normal range for nutritional measures have better lung function and survival outcomes (29).

The CFQ-R is a reliable and validated instrument for the assessment of patient-reported quality of life in CF, including for pediatric patients (30). We found that, from Week 8 onward, mean respiratory domain scores improved more than the minimal clinically important difference in CF patient populations aged 6 years and above (4 points; determined by analysis of two open-label studies of inhaled tobramycin use in patients with CF) (31).

In our patient population we noted fairly normal baseline percent predicted FEV_1 values but abnormal baseline $LCI_{2.5}$ values. This has been noted in previous studies in children with CF and has been taken as evidence of small airway disease that is amenable to assessment by LCI but falls below the limits of detection of standard spirometry. In CF, as a consequence of heterogeneous obstruction of small airways caused by mucus plugging, the distribution of ventilation is significantly affected, and this has an important effect on multiple-breath washout test indices such as the LCI (32). The sensitivity of LCI to small airway disease has been further validated by studies demonstrating better agreement of LCI with high-resolution computed tomography findings, as opposed to spirometry (33). In addition, LCI values early in life have been shown to predict future pulmonary function abnormalities (34). LCI has been recommended for use in trials involving young patients with CF and patients with early or mild lung disease (35), and it has been used to demonstrate the efficacy of ivacaftor alone in patients with at least one *G551D* mutant allele and well-preserved lung function (36). Although we found no significant improvement in percent predicted FEV_1, we did detect significant improvements in $LCI_{2.5}$ at all on-treatment visits versus baseline. Although a minimal clinically important difference is yet to be established for this measure, it has been recommended that to be considered clinically significant, treatment effects should be larger than coefficients of reliability for replicate measurements (35). The mean improvement in $LCI_{2.5}$ observed at the Week 4 visit in the present study (a reduction from baseline of 1.08) was above previously reported coefficients of reliability in patients

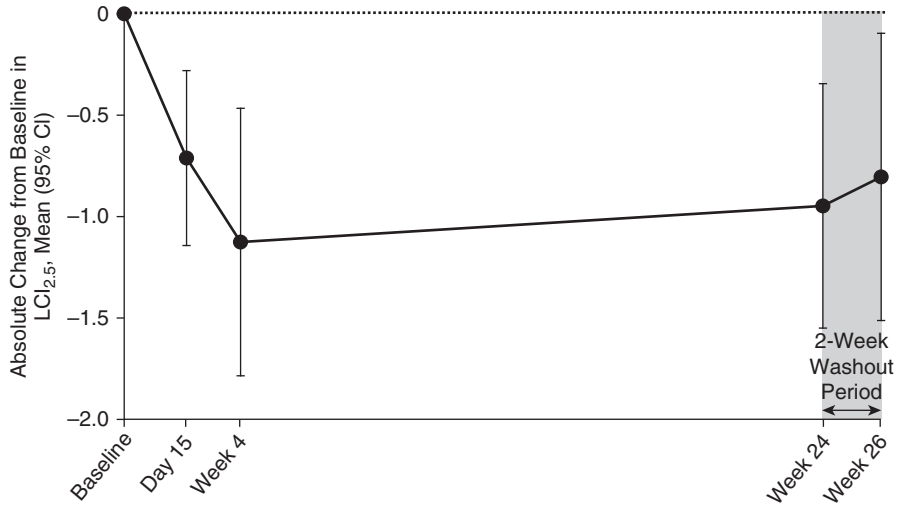

Figure 6. Absolute change from baseline in $LCI_{2.5}$. Raw summary statistics (unadjusted for mixed-effects models for repeated measures covariates) are shown for absolute change from baseline at study visits and Week 26 follow-up visit. Decrease in $LCI_{2.5}$ indicates improvement. CI = confidence interval; $LCI_{2.5}$ = lung clearance index (lung volume turnover required to reach 2.5% of starting N_2 concentration).

with CF in this age group undergoing N_2-based $LCI_{2.5}$ testing (intratest coefficient of reliability, 1.00; intertest, 0.96) (37). Further, this level of improvement is comparable to the magnitude of effect reported in previous trials assessing the effect on $LCI_{2.5}$ of drugs known to be efficacious in CF (38, 39). The noted effects on LCI merit further investigation through larger randomized trials of longer duration to assess the magnitude of effect compared with a control group, as well as to evaluate for the sustainability of any effects with prolonged exposure. Such studies would also provide additional information on the relevance of changes in LCI in relation to other clinical outcomes.

In conclusion, in this study, combination therapy with lumacaftor/ivacaftor was generally well tolerated in patients aged 6–11 years with CF who were homozygous for the *F508del-CFTR* mutation, with a safety profile consistent with those in previous studies of adolescent and adult patients with this mutation. Respiratory events were observed with lower frequency than in older patients, were not temporally related to treatment initiation in most cases, and did not lead to treatment discontinuation in any patients. Even though we did not observe significant improvement in percent predicted FEV_1 in this young population with relatively well-preserved spirometric measures of lung function, we did detect significant improvement in the LCI in a subset of patients, suggesting that it may be a more sensitive measure with which to evaluate a treatment effect in a young population with normal to near-normal spirometric measures. Sweat chloride determinations supported a marked increase in CFTR activity while patients were receiving lumacaftor/ivacaftor, and improved BMI was also observed. Lumacaftor/ivacaftor therapy positively impacted the respiratory domain of patients' self-reported quality of life. Although a limitation of our study is its open-label design, the rapid onset of detectable responses in sweat chloride as a surrogate of CFTR function, as well as the magnitude of the individual responses observed (Figure E1), along with a return to baseline values after the end of therapy, give confidence in the conclusion that these effects were study drug related. Special emphasis must be placed on the persistence of improved $LCI_{2.5}$ after the end of treatment. Given the relatively large cross-sectional area offered by the small airways, this persistence could be due to a potential need for a longer latency period before significant and sufficient peripheral airway obstruction recurs and noticeable detrimental changes are detected. Overall, the findings of this study demonstrate the safety profile of lumacaftor/ivacaftor therapy in patients aged 6–11 years with CF who are homozygous for the *F508del-CFTR* mutation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the patients and their families, the study investigators, and the study coordinators for their roles in the study. Editorial coordination and support were provided by Dhrupad Patel, Pharm.D., who is an employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. Medical writing and editorial support were provided by Jeremy Kennard, Ph.D., Mary Kacillas, and Paula Stuckart of Ashfield Healthcare Communications, which received funding from Vertex Pharmaceuticals Incorporated.

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