ORIGINAL ARTICLE

Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for *F508del* and a Minimal Function Mutation

A Phase 3b, Randomized, Placebo-controlled Study

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Abstract

Rationale: The triple-combination regimen elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in children aged 6 through 11 years with cystic fibrosis and at least one *F508del-CFTR* allele in a phase 3, open-label, single-arm study.

Objectives: To further evaluate the efficacy and safety of ELX/TEZ/IVA in children 6 through 11 years of age with cystic fibrosis heterozygous for *F508del* and a minimal function *CFTR* mutation (*F*/MF genotypes) in a randomized, double-blind, placebo-controlled phase 3b trial.

Methods: Children were randomized to receive either ELX/TEZ/IVA ($n = 60$) or placebo ($n = 61$) during a 24-week treatment period. The dose of ELX/TEZ/IVA administered was based on weight at screening, with children <30 kg receiving ELX 100 mg once daily, TEZ 50 mg once daily, and IVA 75 mg every 12 hours, and children ⩾30 kg receiving ELX 200 mg once daily, TEZ 100 mg once daily, and IVA 150 mg every 12 hours (adult dose).

Measurements and Main Results: The primary endpoint was absolute change in lung clearance $index_{2.5}$ from baseline through Week 24. Children given ELX/TEZ/IVA had a mean decrease in lung clearance $index_{2.5}$ of 2.29 units (95% confidence interval [CI], 1.97–2.60) compared with 0.02 units (95% CI, −0.29 to 0.34) in children given placebo (between-group treatment difference, −2.26 units; 95% CI, −2.71 to −1.81; $P < 0.0001$). ELX/TEZ/IVA treatment also led to improvements in the secondary endpoint of sweat chloride concentration (between-group treatment difference, −51.2 mmol/L; 95% CI, −55.3 to −47.1) and in the other endpoints of percent predicted FEV_1 (between-group treatment difference, 11.0 percentage points; 95% CI, 6.9–15.1) and Cystic Fibrosis Questionnaire-Revised Respiratory domain score (between-group treatment difference, 5.5 points; 95% CI, 1.0–10.0) compared with placebo from baseline through Week 24. The most common adverse events in children receiving ELX/TEZ/IVA were headache and cough (30.0% and 23.3%, respectively); most adverse events were mild or moderate in severity.

Conclusions: In this first randomized, controlled study of a cystic fibrosis transmembrane conductance regulator modulator conducted in children 6 through 11 years of age with *F*/MF genotypes, ELX/TEZ/IVA treatment led to significant improvements in lung function, as well as robust improvements in respiratory symptoms and cystic fibrosis transmembrane conductance regulator function. ELX/TEZ/IVA was generally safe and well tolerated in this pediatric population with no new safety findings.

Keywords: cystic fibrosis; elexacaftor; tezacaftor; ivacaftor; children

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At a Glance Commentary

Scientific Knowledge on the Subject: A previous phase 3 open-label study demonstrated the safety and efficacy of the CFTR modulator regimen elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in children aged 6 through 11 years with cystic fibrosis (CF) and at least one *F508del* allele. These results supported the use of ELX/TEZ/IVA as an effective treatment in the early stages of CF disease.

What This Study Adds to the Field: To further assess the efficacy and safety of ELX/TEZ/IVA in this pediatric population, we conducted a randomized, controlled study in children heterozygous for *F508del* and a minimal function mutation (*F*/MF genotypes). ELX/TEZ/IVA treatment led to statistically significant improvements in lung function, as well robust improvements in respiratory symptoms and CFTR function, compared with placebo, with no new safety findings. Our results demonstrate the ability of ELX/TEZ/IVA treatment to alter the natural trajectory of CF disease in children.

Cystic fibrosis (CF) is an autosomal recessive disease that results from mutations in the CF transmembrane conductance regulator (*CFTR*) gene (1). More than 1,000 pathogenic *CFTR* mutations have been described (2, 3); the *F508del-CFTR* mutation is the most common of these, being present in nearly 90% of patients with CF in some parts of the world (4). Patients with *F508del-CFTR* mutations have decreases in the quantity and function of the CFTR anion channel present at epithelial cell surfaces, leading to diverse clinical consequences that manifest early in life and include pancreatic insufficiency, growth impairment, and progressive lung disease (5–9).

CFTR modulators are small-molecule therapeutics designed to address the underlying cause of CF (8, 9). CFTR correctors, such as elexacaftor (ELX) and tezacaftor (TEZ), improve CFTR processing and trafficking to epithelial surfaces, whereas CFTR potentiators, such as ivacaftor (IVA), enhance CFTR channel gating (5, 10). In adolescents and adults who are heterozygous for *F508del* and a minimal function *CFTR* mutation (*F*/MF genotypes) or homozygous for *F508del* (*F*/*F* genotype), a triple combination regimen of ELX/TEZ/IVA was shown to be safe and efficacious (11–13). ELX/TEZ/IVA treatment resulted in robust and clinically meaningful improvements in lung function (as assessed by percent predicted FEV_1 [$ppFEV_1$]), respiratory symptoms (as assessed by Cystic Fibrosis Questionnaire-Revised [CRQ-R] respiratory domain score), and CFTR function (as assessed by sweat chloride concentration) in these patients and provided greater efficacy than the previously approved dual combination of TEZ/IVA in patients with the *F*/*F* genotype. These results established ELX/TEZ/IVA as a highly effective treatment for adolescents and adults with CF who have at least one *F508del* allele (14).

The progressive lung disease associated with CF develops early in life, with pulmonary infection, inflammation, and structural lung damage occurring frequently in school-aged children with CF; thus, early treatment is critical to improving clinical outcomes and life expectancy (15–19). Given the substantial clinical benefits of ELX/TEZ/IVA observed in adults and adolescents with at least one *F508del* allele (11, 12), an open-label phase 3 study was conducted to assess the safety, pharmacokinetics, and efficacy of ELX/TEZ/IVA in pediatric patients aged 6 through 11 years with either *F*/MF or *F*/*F* genotypes (20). In this trial, ELX/TEZ/IVA was generally safe and well tolerated, indicating a safety profile in 6- through 11-year-olds consistent with that previously established in adults and adolescents (20). Furthermore, ELX/TEZ/IVA treatment led to improvements in $ppFEV_1$, CFQ-R respiratory domain score, lung clearance $index_{2.5}$ ($LCI_{2.5}$), and sweat chloride concentration. These results suggest that children obtain similar clinical benefits from ELX/TEZ/IVA treatment as older patients, despite having higher baseline lung function and CFQ-R respiratory domain scores than adults and adolescents (20). Because the primary objective of the open-label study in children aged 6 through 11 years was to assess safety, a placebo-controlled trial focused on efficacy was performed to better understand the extent to which ELX/TEZ/IVA treatment ameliorates early airway disease and improves lung function in this pediatric population.

Here, we report results from a 24-week placebo-controlled trial designed to quantify the efficacy of ELX/TEZ/IVA in children 6 through 11 years of age with CF with *F*/MF genotypes. Absolute change in $LCI_{2.5}$ was designated the primary endpoint because LCI derived from multiple-breath washout testing is considered a highly sensitive measure for small airway disease and lung function change in this age group and has been shown to detect treatment responses in children who have normal spirometry values ($ppFEV_1 \geqslant 80$ percentage points) (19, 21–25).

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Author Contributions: 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. M.A.M., M.J., S.M.M., T.G.W., C.E.W., and J.C.D. developed the initial draft of the manuscript with writing assistance from the sponsor. All authors participated in subsequent revisions. All authors approved the final version submitted for publication.

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This article has a related editorial.

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

Methods

Participants, Trial Design, and Oversight

This phase 3b, randomized, double-blind, placebo-controlled, multicenter trial of ELX/TEZ/IVA enrolled children aged 6 through 11 years with CF and *F*/MF genotypes and $LCI_{2.5} \geq 7.5$. The *CFTR* genotype was confirmed as part of screening. Placebo was considered the most appropriate comparator because, at the time the study was conducted, there was no approved CFTR modulator for children 6 through 11 years of age with *F*/MF genotypes. For additional details on eligibility criteria, including a list of qualifying MF mutations, *see* Table E1 in the online supplement.

Children were randomized (1:1) to receive either ELX/TEZ/IVA or a placebo over a 24-week treatment period (Figure E1). Randomization was stratified by $LCI_{2.5}$ at screening (<10 vs. ≥ 10) and weight at screening (<30 kg vs. ≥ 30 kg). Dosing was based on weight at screening: children weighing <30 kg received ELX 100 mg once daily, TEZ 50 mg once daily, and IVA 75 every 12 hours (50% of adult dose), whereas children weighing ≥ 30 kg received ELX 200 mg once daily, TEZ 100 mg once daily, and IVA 150 every 12 hours (full adult dose).

The trial was designed by Vertex Pharmaceuticals Incorporated in collaboration with the authors. For each child enrolled in the study, informed consent was provided by a parent or legal guardian; assent was obtained from the participants in accordance with local regulations. Safety was monitored by an independent data monitoring committee. Vertex Pharmaceuticals performed data collection and analysis in collaboration with the authors and the VX19–445–116 Study Group. Authors had full access to trial data after the final database lock, critically reviewed the manuscript, and approved it for final submission. The investigators vouch for the accuracy and completeness of the data generated at their sites, and the investigators and Vertex Pharmaceuticals vouch for the fidelity of the trial to the protocol.

As this study was initiated during the coronavirus disease 2019 (COVID-19) pandemic, a global protocol addendum provided participants with options to minimize the risk of COVID-19 exposure that might occur through travel. Implemented measures, as permitted by country and local regulations, enabled remote consent, remote monitoring visits, in-home assessments, and shipment of study drugs to the homes of participants.

Outcome Measures

The primary endpoint was absolute change in $LCI_{2.5}$ from baseline through Week 24. The EcoMedics Exhalyzer-D multiple-breath washout device with Spiroware Version 3.1.6 was used to determine individual LCI results. Secondary endpoints were absolute change in sweat chloride concentration from baseline through Week 24 and safety and tolerability as assessed by adverse events (AEs), clinical laboratory values, electrocardiograms, vital signs, pulse oximetry, and ophthalmologic examinations. Other efficacy endpoints included absolute changes in $ppFEV_1$ and CFQ-R respiratory domain score from baseline through Week 24. A *post hoc* analysis was conducted to assess the proportion of children achieving sweat chloride concentrations <60 mmol/L and <30 mmol/L.

Statistical Analysis

The primary null hypothesis tested was that the mean absolute change in $LCI_{2.5}$ from baseline through Week 24 was the same for the two treatment groups (ELX/TEZ/IVA and placebo). A sample size of 49 children completing treatment in each group (98 total children completing treatment in the study) had approximately 90% power for $LCI_{2.5}$ hypothesis testing (assuming a within-group standard deviation of 1.5 and a treatment difference of -1.0 between the ELX/TEZ/IVA and placebo groups) on the basis of a 2-sided, 2-sample *t* test at a significance level of 0.05. The target for enrollment was 108 participants, allowing for 10% dropout during the treatment period. A mixed-effects model for repeated measures was used to analyze absolute changes in $LCI_{2.5}$, sweat chloride concentration, $ppFEV_1$, and CFQ-R respiratory domain score. The model included treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline $LCI_{2.5}$ and weight at screening visit (<30 kg vs. ≥ 30 kg) as covariates. The primary result obtained from the model was the estimated treatment difference through Week 24 (defined as the average of Weeks 4, 8, 16, and 24). The main analyses for safety included all data collected up to Week 24 in the treatment period and included both in-clinic and at-home assessments. Further details on the statistical analyses are provided in the online supplement.

Results

Population

The trial was conducted at 34 sites in Australia, Canada, Denmark, France, Germany, Israel, Netherlands, Spain, Switzerland, and the United Kingdom from 19 June 2020 to 17 May 2021. Overall, 121 children were randomized and received 1 or more doses of either ELX/TEZ/IVA or placebo in the 24-week treatment period: 60 children received ELX/TEZ/IVA, and 61 children received placebo (Figure 1). One child (1.7%) discontinued ELX/TEZ/IVA because of an AE of rash. The baseline demographics and clinical characteristics were similar between the two treatment groups (Tables 1 and E2).

Efficacy

The primary endpoint of this study was absolute change in $LCI_{2.5}$ from baseline

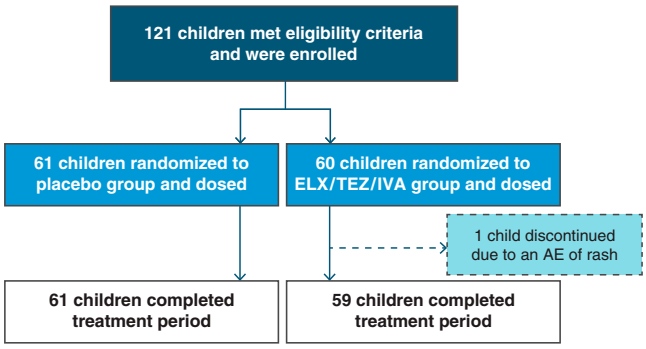

Figure 1. Participant disposition diagram. AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor.

Table 1. Demographics and Clinical Characteristics of the Participants at Baseline*

	Placebo *n* = 61	ELX/TEZ/IVA *n* = 60
Female sex, *n* (%)	35 (57.4)	35 (58.3)
Age at baseline, mean (SD), y	9.2 (1.7)	9.1 (1.8)
Race, *n* (%)†		
White	42 (68.9)	45 (75.0)
Black or African American	0 (0)	1 (1.7)
Asian	0 (0)	1 (1.7)
American Indian or Alaska Native	0 (0)	1 (1.7)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)
Other	1 (1.6)	0 (0)
Not collected per local regulations	18 (29.5)	11 (18.3)
Ethnicity, *n* (%)		
Hispanic or Latino	0 (0)	1 (1.7)
Not Hispanic or Latino	42 (68.9)	48 (80.0)
Not collected per local regulations	19 (31.1)	11 (18.3)
Geographic region, *n* (%)		
Europe	49 (80.3)	43 (71.7)
Other countries (Australia, Canada, Israel)	12 (19.7)	17 (28.3)
Weight, mean (SD), kg	29.8 (8.6)	29.1 (7.6)
Weight distribution, *n* (%)		
<30 kg	38 (62.3)	39 (65.0)
⩾30 kg	23 (37.7)	21 (35.0)
Weight-for-age *z*-score, mean (SD)	−0.29 (0.96)	−0.27 (0.99)
Height, mean (SD), cm	134.6 (13.3)	132.3 (11.7)
Height-for-age *z*-score, mean (SD)	0.01 (1.26)	−0.17 (1.02)
BMI, mean (SD), kg/m^2	16.11 (2.32)	16.33 (1.84)
BMI-for-age *z*-score, mean (SD)	−0.39 (0.92)	−0.17 (0.85)
$LCI_{2.5}$, mean (SD), units	9.75 (1.95)	10.26 (2.22)
Sweat chloride concentration, mean (SD), mmol/L	102.6 (8.6)	102.8 (10.0)
$ppFEV_1$, mean (SD)	87.2 (15.8)	91.4 (13.8)
$ppFEV_1$ category, *n* (%)		
<70	10 (16.4)	4 (6.7)
⩾70 to ⩽90	23 (37.7)	20 (33.3)
>90	28 (45.9)	36 (60.0)
CFQ-R respiratory domain score (child's version), mean (SD) points‡	82.7 (14.1)	85.7 (11.7)

Definition of abbreviations: BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; $LCI_{2.5}$ = lung clearance index$_{2.5}$; $ppFEV_1$ = percent predicted FEV_1.

*Baseline was defined as the most recent nonmissing measurement before the first dose of the study drug in the treatment period.

†The race categories may sum to more than 100% because each participant could indicate more than 1 race.

‡Child's version of CFQ-R was used in the assessment. Scores for the CFQ-R respiratory domain range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status.

through Week 24. Mean $LCI_{2.5}$ at baseline was 10.26 units (standard deviation [SD], 2.22) in the ELX/TEZ/IVA group and 9.75 units (SD, 1.95) in the placebo group (Table 1). Children who received ELX/TEZ/IVA had a mean change in $LCI_{2.5}$ of −2.29 units (95% confidence interval [CI], −2.60 to −1.97), whereas children who received placebo had a mean change of −0.02 units (95% CI, −0.34 to 0.29); the between-group treatment difference was −2.26 units (95% CI, −2.71 to −1.81; $P < 0.0001$) (Table 2 and Figure 2A).

An *ad hoc* subgroup analysis showed the mean between-group treatment difference in $LCI_{2.5}$ was −1.69 (95% CI, −2.12 to −1.26) in children with $LCI_{2.5}$ <10 at screening and −2.79 (95% CI, −3.68 to −1.90) in children with an $LCI_{2.5}$ ⩾10 at screening (Table E3). Absolute changes in sweat chloride concentration (secondary endpoint), $ppFEV_1$ (other endpoint), and CFQ-R respiratory domain score (other endpoint) were also assessed. Mean sweat chloride concentration at baseline was 102.8 mmol/L (SD, 10.0) in the ELX/TEZ/IVA group and 102.6 mmol/L (SD, 8.6) in the placebo group (Table 1). Children given ELX/TEZ/IVA had a mean change in sweat chloride concentration of −52.1 mmol/L (95% CI, −55.0 to −49.2) compared with a mean change of −0.9 mmol/L (95% CI, −3.8 to 2.0) in children given placebo (between-group treatment difference, −51.2 mmol/L; 95% CI, −55.3 to −47.1; nominal $P < 0.0001$) from baseline through Week 24 (Table 2 and Figure 2B). Mean $ppFEV_1$ at baseline was 91.4 percentage points (SD, 13.8) in the ELX/TEZ/IVA group and 87.2 percentage points (SD, 15.8) in the placebo group (Table 1). ELX/TEZ/IVA treatment resulted in a mean change in $ppFEV_1$ of 9.5 percentage points (95% CI, 6.6–12.4), whereas there was a mean change in $ppFEV_1$ of −1.5 percentage points (95% CI, −4.4 to 1.4) in children given placebo (between-group treatment difference, 11.0 percentage points; 95% CI, 6.9–15.1; nominal $P < 0.0001$) from baseline through Week 24 (Table 2 and Figure 2C). The mean CFQ-R respiratory domain score at baseline was 85.7 points (SD, 11.7) in the ELX/TEZ/IVA group and 82.7 points (SD, 14.1) in the placebo group (Table 1). ELX/TEZ/IVA treatment resulted in a mean increase in CFQ-R respiratory domain score of 5.9 points (95% CI, 2.8–9.1) compared with a mean increase of 0.5 points (95% CI, −2.7 to 3.6) in children receiving placebo (between-group treatment difference, 5.5; 95% CI, 1.0–10.0; nominal $P = 0.0174$) from baseline through Week 24 (Table 2 and Figure 2D). Mean sweat chloride concentrations after treatment of <60 mmol/L and <30 mmol/L through Week 24 were assessed as a *post hoc* analysis. Overall, 49 of 60 children (81.7%) treated with ELX/TEZ/IVA had sweat chloride concentrations <60 mmol/L, and 2 of 60 children (3.3%) had sweat chloride concentrations <30 mmol/L through Week 24; no children who received placebo had sweat chloride concentrations <60 mmol/L through Week 24 (Figure E2 and Table E4).

Safety

Overall, 48 children (80%) who received ELX/TEZ/IVA and 57 children (93.4%) who received placebo had AEs (Table 3). The majority had AEs that were mild or moderate in severity and generally consistent with manifestations of CF. The most common AEs (⩾15% of children) in the ELX/TEZ/IVA group were headache (30%) and cough (23.3%) and in the placebo group were cough (42.6%), abdominal pain (27.9%), infective pulmonary exacerbation of CF (26.2%), headache (19.7%), and oropharyngeal pain (19.7%). Serious AEs

Table 2. Primary, Secondary, and Other Efficacy Endpoints

	Placebo $n = 61$	ELX/TEZ/IVA $n = 60$
Primary endpoint: absolute change in $LCI_{2.5}$, units		
Baseline, mean (SD)*	9.75 (1.95)	10.26 (2.22)
Absolute change through Week 24, LS mean (95% CI)	−0.02 (−0.34 to 0.29)	−2.29 (−2.60 to −1.97)
Between-group difference (95% CI)	−2.26 (−2.71 to −1.81) $P < 0.0001$	
Secondary endpoint: absolute change in sweat chloride, mmol/L		
Baseline, mean (SD)*	102.6 (8.6)	102.8 (10.0)
Absolute change through Week 24, LS mean (95% CI)	−0.9 (−3.8 to 2.0)	−52.1 (−55.0 to −49.2)
Between-group difference (95% CI)	−51.2 (−55.3 to −47.1) $P < 0.0001$†	
Other endpoint: absolute change in $ppFEV_1$, percentage points		
Baseline, mean (SD)*	87.2 (15.8)	91.4 (13.8)
Absolute change through Week 24, LS mean (95% CI)	−1.5 (−4.4 to 1.4)	9.5 (6.6 to 12.4)
Between-group difference (95% CI)	11.0 (6.9 to 15.1) $P < 0.0001$†	
Other endpoint: absolute change in CFQ-R respiratory domain score, points		
Baseline, mean (SD)*	82.7 (14.1)	85.7 (11.7)
Absolute change through Week 24, LS mean (95% CI)	0.5 (−2.7 to 3.6)	5.9 (2.8 to 9.1)
Between-group difference (95% CI)	5.5 (1.0 to 10.0) $P = 0.0174$†	

Definition of abbreviations: CFQ-R = Cystic Fibrosis Questionnaire Revised; CI = confidence interval; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; $LCI_{2.5}$ = lung clearance index$_{2.5}$; LS = least-squares; $ppFEV_1$ = percent predicted FEV_1; SD = standard deviation.
*Baseline was defined as the most recent nonmissing measurement before the first dose of the study drug in the treatment period.
†*P* values are considered to be nominal.

occurred in 4 children (6.7%) receiving ELX/TEZ/IVA and in 9 children (14.8%) receiving a placebo. One child (1.7%) who received ELX/TEZ/IVA had a serious AE of rash that resolved after treatment discontinuation.

On the basis of previous experience with ELX/TEZ/IVA, including phase 3 trials in participants 12 years of age or older and in children 6 through 11 years of age (11, 12, 20), data related to aminotransferases, rash events, blood pressure, and creatine kinase were reviewed. Among children who received ELX/TEZ/IVA, elevated concentrations of alanine aminotransferase and/or aspartate aminotransferase more than three times the upper limit of normal (ULN) occurred in eight children (13.6%), with three (5.1%) having concentrations more than five times the ULN and one (1.7%) having concentrations more than eight times the ULN. Among children who received placebo, three (4.9%) had elevated concentrations of alanine aminotransferase and/or aspartate aminotransferase more than three times the ULN, with one child (1.6%) having concentrations more than five times the ULN and no children having concentrations more than eight times the ULN (Table E5). No children had alanine aminotransferase and/or aspartate aminotransferase concentrations more than three times the ULN concurrent with total bilirubin concentrations more than two times ULN. Adverse events of elevated aminotransferases were reported in six children (10.0%) who received ELX/TEZ/IVA and in three children (4.9%) who received placebo, all of which were mild or moderate in severity and none of which were considered serious or led to treatment discontinuation.

Eight children (13.3%) who received ELX/TEZ/IVA and three children (4.9%) who received placebo had rash events (Table E6). Rash events comprised a group AE term that included preferred terms of rash, rash erythematous, rash maculopapular, rash papular, skin exfoliation, and urticaria. Among children who had rash events, most had events that were mild or moderate in severity. One child (1.7%) had a serious AE of rash that developed on Day 8 of ELX/TEZ/IVA treatment. This AE resolved after study drug discontinuation and treatment with antihistamines and topical steroids. No other children discontinued treatment because of rash events.

In children who received ELX/TEZ/IVA, the mean change from baseline in systolic blood pressure (mm Hg) ranged from 0.1 (Day 15) to 2.6 (Week 8), and in diastolic blood pressure ranged from −2.1 (Day 15) to 1.1 (Week 8) (Table E7). In children who received placebo, the mean change from baseline in systolic blood pressure ranged from 0.0 (Week 4) to 2.6 (Week 16), and in diastolic blood pressure ranged from −0.3 (Week 4) to 1.3 (Week 8). No children had AEs of blood pressure increased. No children had creatine kinase concentrations more than five times the ULN (Table E8). There were no notable safety findings in other clinical or laboratory assessments.

Discussion

The efficacy and safety of ELX/TEZ/IVA were evaluated in a 24-week randomized, double-blind, placebo-controlled trial in children 6 through 11 years of age with *F*/MF genotypes. Treatment with ELX/TEZ/IVA resulted in significant improvements in $LCI_{2.5}$ as well as robust improvements in $ppFEV_1$, CFQ-R respiratory domain score, and sweat chloride concentration compared with placebo. Safety data were consistent with the established safety profile for ELX/TEZ/IVA, with no new safety concerns observed.

Impaired lung function is a hallmark of CF disease progression that begins early in life (17). In adults and adolescents with CF, lung function impairment is typically assessed using spirometry. However, in children with CF, baseline FEV_1 is often

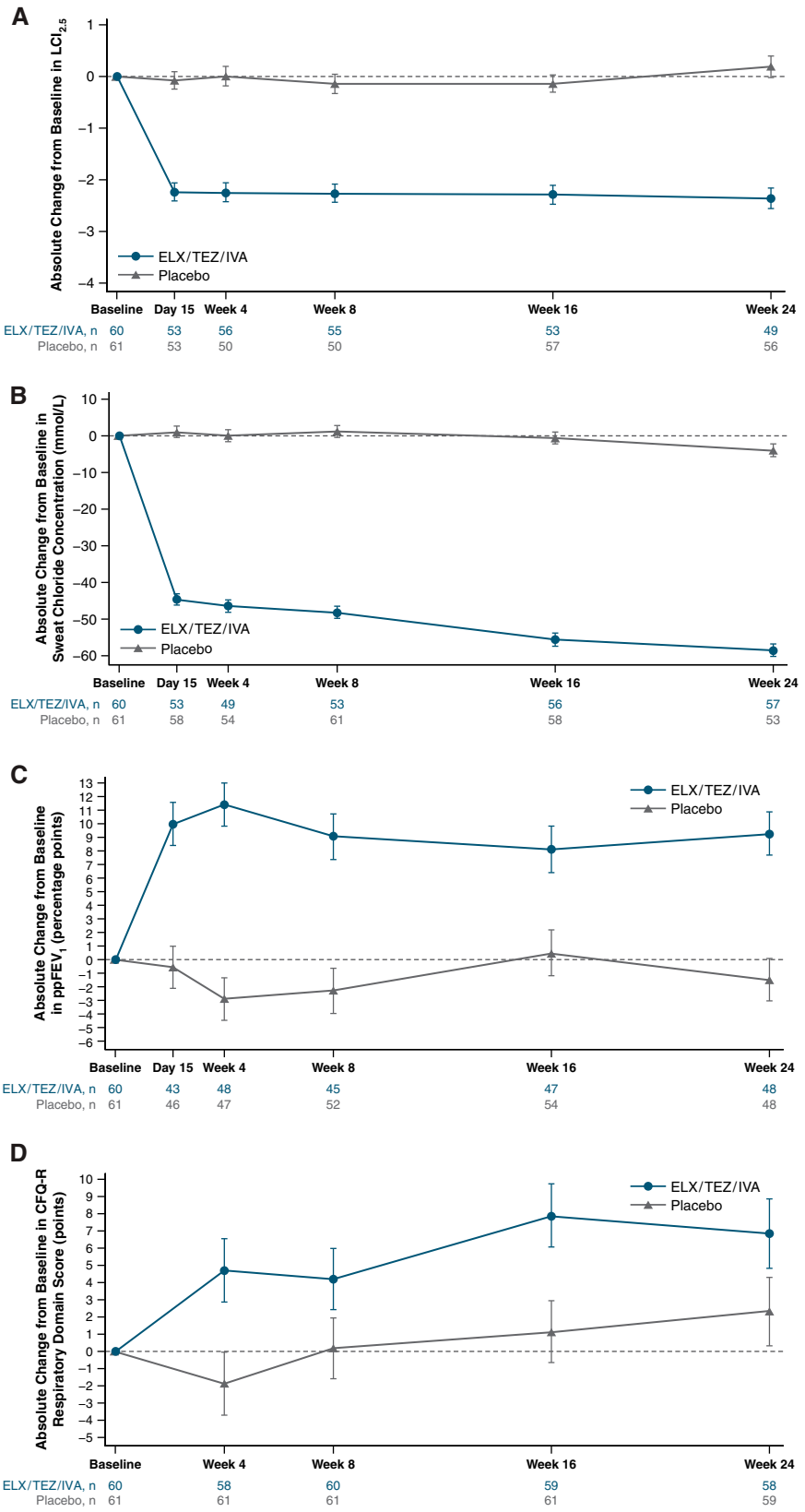

Figure 2. Efficacy results by visit. (*A*) Absolute change in $LCI_{2.5}$ from baseline at each visit. Lower values indicate decreased airway obstruction and improved homogeneity of ventilation. (*B*) Absolute change in sweat chloride concentration from baseline at each visit; lower values indicate increased CFTR function. (*C*) Absolute change in $ppFEV_1$ from baseline at each visit. (*D*) Absolute change in the respiratory domain score on

within the normal range (26), as was seen in the children enrolled in this study. $LCI_{2.5}$, a measure of ventilation inhomogeneity derived from the multiple-breath washout test, can detect early changes in lung function and small airway disease and is therefore considered a more sensitive predictor of lung disease progression than FEV_1 in children with CF (27, 28). A longitudinal natural history study showed that children 6 through 11 years of age with CF who were not treated with a CFTR modulator had an annual increase in $LCI_{2.5}$ of 0.21 units (29). Treatment with the CFTR modulators TEZ/IVA (within-group change −0.51 units at Week 8) and LUM/IVA (within-group change −0.88 at Week 24) was associated with improved $LCI_{2.5}$ in children 6 through 11 years (30, 31). In the current study, abnormal $LCI_{2.5}$ (⩾7.5) values were an inclusion criterion, indicating the presence of early small airway disease in these children. In contrast to the natural history data, as well as the TEZ/IVA and LUM/IVA data described above, ELX/TEZ/IVA treatment resulted in a statistically significant improvement in $LCI_{2.5}$ of −2.26 units from baseline through Week 24 compared with placebo, which was rapid (occurring by Day 15) and sustained. Although the minimal clinically important difference for $LCI_{2.5}$ has not been defined, our results indicate ELX/TEZ/IVA treatment is associated with a robust and sustained improvement in small airway function and pulmonary ventilation in children with CF.

After the data from this clinical trial had been analyzed, the software for the EcoMedics Exhalyzer-D multiple-breath washout device, used for $LCI_{2.5}$ assessment in the current study, was updated to correct for cross-sensitivity in the device's oxygen and carbon dioxide sensors that would otherwise result in overestimation of the nitrogen concentration (32). The effect of this software update on the interpretation of LCI results was assessed in a recent report that reanalyzed data sets from six previous studies involving 1,036 multiple-breath washout tests (33). As expected, the correction algorithm resulted in somewhat lower LCI values but did not change their interpretation or the significance of treatment effects (33). In light of the robust $LCI_{2.5}$ treatment effect seen with ELX/TEZ/IVA in the current study and the results of the reanalysis performed with updated software in the study above, it is highly unlikely that a reanalysis of the LCI data would alter the interpretation of the results obtained with the prespecified analysis as reported here.

Children in this study also had substantial improvements in both $ppFEV_1$ and CFQ-R respiratory domain score. Decreases in FEV_1 are a sensitive indicator of airflow limitation in larger conducting airways that are often seen in adolescents and adults with CF, corresponding to the degree of airway obstruction determined by wall thickening and mucus plugging (34). In this study, despite preserved spirometry at baseline, children given ELX/TEZ/IVA had a mean increase of 11.0 percentage points in $ppFEV_1$ compared with placebo from baseline through Week 24, similar to the improvement observed in older patients with *F*/MF genotypes treated with ELX/TEZ/IVA who had substantially lower baseline $ppFEV_1$ values as well as in the open-label study of ELX/TEZ/IVA in this age group (11, 20). This result indicates that, in addition to the substantial improvement in small airway function seen on the basis of the improvement in $LCI_{2.5}$ with ELX/TEZ/IVA treatment, these children also had improved large airway function, further confirming the robust clinical benefit of ELX/TEZ/IVA treatment on lung function in this pediatric population. Furthermore, children given ELX/TEZ/IVA also had a mean increase of 5.5 points in CFQ-R respiratory domain score compared with placebo, reflecting improved respiratory symptoms and exceeding the minimal clinically important difference of four points (35). These findings corroborate the marked improvement in respiratory status indicated by improved $LCI_{2.5}$ as the primary endpoint.

Table 3. Adverse Events*

	Placebo *n* = 61, *n* (%)	ELX/TEZ/IVA *n* = 60, *n* (%)
Any AE	57 (93.4)	48 (80.0)
AE by maximum severity†		
Mild	26 (42.6)	30 (50.0)
Moderate	29 (47.5)	16 (26.7)
Severe	2 (3.3)	2 (3.3)
Serious AE	9 (14.8)	4 (6.7)
Serious related AE	1 (1.6)	1 (1.7)‡
AE leading to death	0 (0)	0 (0)
AE leading to discontinuation	0 (0)	1 (1.7)‡
Most prevalent AEs§		
Headache	12 (19.7)	18 (30.0)
Cough	26 (42.6)	14 (23.3)
Nasopharyngitis	9 (14.8)	7 (11.7)
Productive cough	6 (9.8)	7 (11.7)
Rhinorrhea	7 (11.5)	7 (11.7)
Rash	3 (4.9)	6 (10.0)
Abdominal pain	17 (27.9)	5 (8.3)
Oropharyngeal pain	12 (19.7)	3 (5.0)
Infective pulmonary exacerbation of cystic fibrosis	16 (26.2)	1 (1.7)

Definition of abbreviations: AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor.
*A participant with multiple events within a category was counted only once in that category.
†Severity was determined by the investigator observing the event.
‡One child had a serious AE of rash that was considered possibly related to ELX/TEZ/IVA and resolved after study discontinuation.
§Only AEs that occurred in ⩾10% of participants are listed; the listing is according to the preferred term (Medical Dictionary for Regulatory Activities version 24.0).

Figure 2. (*Continued*). the CFQ-R (child's version) from baseline at each visit; scores normalized to a 100-point range, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms. Data are least-squares means based on a mixed-effects model for repeated measures; I-bars indicate the standard error of the mean, and the dashed horizontal line corresponds to the baseline. The sample size shown below the *x*-axis is the number of children at the time point with evaluable in-clinic data. CFQ-R = Cystic Fibrosis Questionnaire Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; $LCI_{2.5}$ = lung clearance index$_{2.5}$; $ppFEV_1$ = percent predicted FEV_1.

Sweat chloride concentration provides a direct measure of systemic CFTR function (6). A recent observational study in adolescents and adults with CF and at least one *F508del* allele showed improvements in sweat chloride concentration achieved with ELX/TEZ/IVA treatment were associated with improvements in CFTR function in airway and intestinal epithelia (36). As pediatric patients with CF often have clinical manifestations of the disease beyond the lung, including exocrine pancreatic insufficiency and malabsorption, it is important to understand the systemic impact of modulator therapies on CFTR function. In the previous open-label study in children 6 through 11 years of age, a subgroup analysis showed ELX/TEZ/IVA treatment improved sweat chloride concentrations in children with *F*/MF genotypes, with a mean change of −55.1 mmol/L from baseline through Week 24 (20). In addition, 80% of children achieved sweat chloride concentrations <60 mmol/L and 5.7% achieved sweat chloride concentrations <30 mmol/L (20). In this study, treatment with ELX/TEZ/IVA resulted in similar rapid and robust reductions in sweat chloride concentration through Week 24 compared with placebo (treatment difference, −51.2 mmol/L); no children in the placebo group achieved sweat chloride concentrations <60 mmol/L, whereas 81.7% of children treated with ELX/TEZ/IVA achieved sweat chloride concentrations <60 mmol/L (nominal $P < 0.0001$ vs. placebo) and 3.3% achieved sweat chloride concentrations <30 mmol/L (nominal $P < 0.2438$ vs. placebo). These results demonstrate that ELX/TEZ/IVA treatment substantially improves CFTR function in this age group.

Treatment with ELX/TEZ/IVA was generally safe and well tolerated, with a safety profile consistent with the previous open-label study in children 6 through 11 years of age, as well as studies in adolescents and adults (11, 12, 20). The incidence of transaminase elevation and rash events associated with ELX/TEZ/IVA treatment was consistent with the open-label study in children 6 through 11 years of age, and as seen previously, children had no meaningful changes in blood pressure.

One potential limitation of the current study, as well as other clinical studies in participants with *F508del-CFTR* mutations, is the relative paucity of individuals from minority groups, a consequence of the *F508del-CFTR* mutation being less common in these populations and individuals from minority groups being more likely to have an unknown *CFTR* mutation or a deletion or duplication mutations that can be missed on DNA panels (37). In addition, in the current study, up to 31.1% of participants in the placebo group and 18.3% of participants in the ELX/TEZ/IVA group were from areas where race and/or ethnicity information was not collected as per local regulations. Although unknown, these participants may have been from different racial backgrounds, including minority groups. However, it is also important to consider that entering clinical trials may be more challenging for minority groups because of critical barriers that have been identified, such as mistrust, lack of comfort and information on the clinical trial process, time and resource constraints, and lack of awareness of clinical trials (38). Finally, part of this study took place during the COVID-19 pandemic, in which social distancing, limitations on social interactions, and mask use could have contributed to a decrease in the background rate of pulmonary exacerbations (39).

Conclusions

In this first randomized controlled study of a CFTR modulator in children 6 through 11 years of age with the *F*/MF genotypes, treatment with ELX/TEZ/IVA led to rapid, statistically significant, and clinically meaningful improvements in lung function compared with placebo. Improvements in respiratory symptoms and CFTR function, similar to those seen in adolescents and adults (11, 12), were observed in children given ELX/TEZ/IVA compared with placebo. ELX/TEZ/IVA was generally safe and well tolerated in this pediatric population with no new safety findings. Taken together, these results demonstrate the ability of ELX/TEZ/IVA treatment to ameliorate early airway disease in CF and alter the natural trajectory of CF disease in children. ■

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