ORIGINAL ARTICLE

Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele

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ABSTRACT

BACKGROUND

Cystic fibrosis is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, and nearly 90% of patients have at least one copy of the Phe508del *CFTR* mutation. In a phase 2 trial involving patients who were heterozygous for the Phe508del *CFTR* mutation and a minimal-function mutation (Phe508del–minimal function genotype), the next-generation CFTR corrector elexacaftor, in combination with tezacaftor and ivacaftor, improved Phe508del CFTR function and clinical outcomes.

METHODS

We conducted a phase 3, randomized, double-blind, placebo-controlled trial to confirm the efficacy and safety of elexacaftor–tezacaftor–ivacaftor in patients 12 years of age or older with cystic fibrosis with Phe508del–minimal function genotypes. Patients were randomly assigned to receive elexacaftor–tezacaftor–ivacaftor or placebo for 24 weeks. The primary end point was absolute change from baseline in percentage of predicted forced expiratory volume in 1 second (FEV_1) at week 4.

RESULTS

A total of 403 patients underwent randomization and received at least one dose of active treatment or placebo. Elexacaftor–tezacaftor–ivacaftor, relative to placebo, resulted in a percentage of predicted FEV_1 that was 13.8 points higher at 4 weeks and 14.3 points higher through 24 weeks, a rate of pulmonary exacerbations that was 63% lower, a respiratory domain score on the Cystic Fibrosis Questionnaire–Revised (range, 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms; minimum clinically important difference, 4 points) that was 20.2 points higher, and a sweat chloride concentration that was 41.8 mmol per liter lower ($P<0.001$ for all comparisons). Elexacaftor–tezacaftor–ivacaftor was generally safe and had an acceptable side-effect profile. Most patients had adverse events that were mild or moderate. Adverse events leading to discontinuation of the trial regimen occurred in 1% of the patients in the elexacaftor–tezacaftor–ivacaftor group.

CONCLUSIONS

Elexacaftor–tezacaftor–ivacaftor was efficacious in patients with cystic fibrosis with Phe508del–minimal function genotypes, in whom previous CFTR modulator regimens were ineffective. (Funded by Vertex Pharmaceuticals; VX17-445-102 ClinicalTrials.gov number, NCT03525444.)

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Cystic fibrosis is a lethal, inherited, autosomal recessive disorder that affects approximately 80,000 people worldwide and is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein that lead to reduced CFTR function.[1-3] *CFTR* codes for an epithelial anion channel that transports both Cl^- and HCO_3^- across epithelial surfaces in the respiratory tract, pancreas, gastrointestinal system, and sweat glands, among other organs.[1,2,4,5] Although there are hundreds of different disease-causing mutations, nearly 90% of persons with cystic fibrosis have at least one copy of the most common mutation, the Phe508del *CFTR* mutation.[6]

The Phe508del *CFTR* mutation causes defective intracellular processing and trafficking and decreased stability, which drastically reduces the quantity of CFTR protein at the apical surface of epithelial cells.[4,7,8] Phe508del CFTR protein also exhibits defective channel gating, which further limits anion transport.[7] To restore Phe508del CFTR function, these molecular defects need to be addressed.

CFTR modulators treat the underlying cause of disease and have improved clinical outcomes in persons with specific *CFTR* mutations.[9-12] These medications include small-molecule correctors that increase cell-surface expression by improving the processing and trafficking of CFTR, as well as small-molecule potentiators that augment channel gating.[13] For persons with cystic fibrosis who are homozygous for the Phe508del *CFTR* mutation, the combination of a single corrector, either lumacaftor or tezacaftor, with the potentiator ivacaftor improves clinical outcomes, including lung function and the rate of pulmonary exacerbations.[9,11] However, neither of these dual combinations is sufficiently effective in persons with cystic fibrosis who have a single Phe508del allele and a second *CFTR* mutation that does not respond to current CFTR modulator therapy.[14,15] Such mutations are termed "minimal function" because of the complete absence of protein production or lack of in vitro responsiveness to ivacaftor and tezacaftor–ivacaftor.[16,17] For these patients, no treatment is available to treat the underlying cause of disease.

We studied the effect of a triple-combination CFTR modulator regimen in patients with cystic fibrosis who have a single Phe508del allele. The combination includes the next-generation corrector elexacaftor plus the corrector tezacaftor and the potentiator ivacaftor to more fully restore the function of Phe508del CFTR.[18] In proof-of-concept trials that evaluated this therapeutic approach,[16,18] elexacaftor–tezacaftor–ivacaftor led to improvements in spirometry, patient-reported respiratory symptoms, and sweat chloride concentration, a marker of CFTR activity, in patients with cystic fibrosis with a single Phe508del allele.[18] To confirm efficacy and safety in this population, we conducted a randomized, placebo-controlled, phase 3 trial (VX17-445-102) of elexacaftor–tezacaftor–ivacaftor in patients who were heterozygous for the Phe508del *CFTR* mutation and a minimal-function mutation (Phe508del–minimal function genotypes).

Methods

Participants, Trial Design, and Oversight

This phase 3, multicenter, randomized, double-blind, placebo-controlled trial of elexacaftor–tezacaftor–ivacaftor involved patients 12 years of age or older with cystic fibrosis and Phe508del–minimal function genotypes. Patients were eligible for inclusion if they had a percentage of predicted forced expiratory volume in 1 second (FEV_1) of 40 to 90% at screening and had stable disease during the 28-day screening period before the first dose of active treatment or placebo. Details of the protocol have been described previously,[17] and the protocol and statistical analysis plan are provided with the full text of this article at NEJM.org. (For complete inclusion and exclusion criteria and details on end points and the statistical analysis, see the Supplementary Appendix, available at NEJM.org; qualifying minimal-function mutations are listed in Table S1 in the Supplementary Appendix.)

The trial had a 4-week screening period and 24-week intervention period (Fig. S1). Patients were randomly assigned in a 1:1 ratio to receive elexacaftor (200 mg once daily) in triple combination with tezacaftor (100 mg once daily) and ivacaftor (150 mg every 12 hours) or matched placebos. Randomization was performed in permuted blocks, with stratification according to percentage of predicted FEV_1 at screening (<70% vs. ≥70%), age at screening (<18 years vs. ≥18 years), and sex. Patients who completed the

intervention period could enroll in an ongoing 96-week open-label extension study in which all patients receive active treatment (VX17-445-105; ClinicalTrials.gov number, NCT03525574).

The trial was designed by Vertex Pharmaceuticals in collaboration with the authors. Data gathering and analysis were performed by Vertex Pharmaceuticals in collaboration with the authors and the VX17-445-102 Study Group. The clinical trial protocol and informed-consent forms were approved by an independent ethics committee at each site. Each enrolled patient, or the patient's legal guardian, provided written informed consent (and assent, when appropriate). Safety was monitored by an independent data monitoring committee. All authors had full access to the trial data after final database lock and critically reviewed the manuscript. The first two authors and last two authors wrote the first draft of the manuscript and made final decisions regarding the content of the submitted manuscript. All authors approved the manuscript for submission. The investigators vouch for the accuracy and completeness of the data generated at their respective sites, and the investigators and Vertex Pharmaceuticals vouch for the fidelity of the trial to the protocol. Confidentiality agreements were in place between the sponsor and each investigative site during the trial.

END POINTS

The primary end point was absolute change from baseline in percentage of predicted FEV_1 at week 4. Key secondary end points were absolute change from baseline in percentage of predicted FEV_1 through week 24, number of pulmonary exacerbations through week 24, absolute change from baseline in sweat chloride concentration through week 24, absolute change from baseline in the Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score (range, 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms; minimum clinically important difference, 4 points) through week 24, absolute change from baseline in body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) at week 24, absolute change from baseline in sweat chloride concentration at week 4, and absolute change from baseline in the CFQ-R respiratory domain score at week 4. Other secondary end points included time to first pulmonary exacerbation through week 24, absolute change from baseline in BMI-for-age z score at week 24, absolute change from baseline in body weight at week 24, and safety and side-effect profile.

STATISTICAL ANALYSIS

Efficacy analyses included all patients who underwent randomization and received at least one dose of elexacaftor–tezacaftor–ivacaftor or placebo. The absolute change from baseline in percentage of predicted FEV_1 at week 4 was analyzed with the use of a mixed-effects model for repeated measures, with change from baseline in percentage of predicted FEV_1 as the dependent variable. The model included trial group, visit, and trial-group–by–visit interaction as fixed effects, with continuous baseline percentage of predicted FEV_1, age at screening (<18 years vs. ≥18 years), and sex as covariates; the model used an unstructured covariance for the within-patient errors. A similar mixed-effects model for repeated measures was applied to analyses of the key secondary end points of percentage of predicted FEV_1 through week 24, sweat chloride concentration, CFQ-R respiratory domain score, and BMI. The number of pulmonary exacerbations was analyzed with the use of a negative binomial-regression model.

A prespecified interim analysis was conducted for the primary end point when at least 140 patients had completed the week 4 visit and at least 100 patients had completed the week 12 visit. A Lan–DeMets alpha-spending function was applied to control the overall type I error rate of 0.05 for the primary end point. Assuming a 5% dropout rate at week 4 and a within-group standard deviation of 7 percentage points, we estimated that an interim-analysis sample size of 70 patients per trial group would provide approximately 98% power to detect a between-group difference of 5.0 points for the mean absolute change from baseline in percentage of predicted FEV_1 at week 4, using a two-sided, two-sample t-test at a significance level of 0.044 based on the alpha-spending function. Safety analyses were descriptive and included all patients who received at least one dose of elexacaftor–tezacaftor–ivacaftor or placebo.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Elexacaftor–Tezacaftor–Ivacaftor (N=200)	Placebo (N=203)
Female sex — no. (%)	96 (48.0)	98 (48.3)
Age		
Mean — yr	25.6±9.7	26.8±11.3
Distribution — no. (%)†		
12 to <18 yr	56 (28.0)	60 (29.6)
≥18 yr	144 (72.0)	143 (70.4)
Geographic region — no. (%)		
North America	118 (59.0)	120 (59.1)
Europe or Australia	82 (41.0)	83 (40.9)
Percentage of predicted FEV_1		
Mean	61.6±15.0	61.3±15.5
Distribution — no. (%)		
<40%‡	18 (9.0)	16 (7.9)
40 to <70%	114 (57.0)	120 (59.1)
70 to ≤90%	66 (33.0)	62 (30.5)
>90%	2 (1.0)	5 (2.5)
Body-mass index	21.49±3.07	21.31±3.14
Sweat chloride concentration — mmol/liter	102.3±11.9	102.9±9.8
CFQ-R respiratory domain score§	68.3±16.9	70.0±17.8

* Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in 1 second.
† Age distribution was calculated on the basis of age at the time of screening.
‡ Although those eligible for enrollment were required to have a percentage of predicted FEV_1 of 40% or more at screening, some participants had a decrease to a value of less than 40% by baseline.
§ Scores on the Cystic Fibrosis Questionnaire–Revised (CFQ-R) are normalized to range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms.

RESULTS

POPULATION

The trial was conducted at 115 sites in 13 countries from June 2018 to April 2019. Overall, 405 patients underwent randomization, and 403 received at least one dose of the trial regimen (200 in the elexacaftor–tezacaftor–ivacaftor group and 203 in the placebo group) (Fig. S2). At baseline, the trial groups were well matched (Table 1 and Table S2). The mean adherence to the trial regimen was more than 98% in both trial groups. All 400 patients who completed the intervention period were enrolled in the open-label extension study.

EFFICACY

Treatment with elexacaftor–tezacaftor–ivacaftor resulted in significant improvement in the primary end point of absolute change in percentage of predicted FEV_1 at week 4, assessed at the interim analysis, with a mean treatment difference of 13.8 points relative to placebo (P<0.001) (Table 2 and Fig. 1A). Sustained improvement in percentage of predicted FEV_1 was seen through week 24 (final analysis), with a mean treatment difference of 14.3 points relative to placebo (P<0.001) (Table 2 and Fig. 1A). The histogram of absolute change in percentage of predicted FEV_1 through week 24 showed marked separation of the two trial groups (Fig. 1B).

Subgroup analysis for absolute change in percentage of predicted FEV_1 at week 4 showed that the mean treatment difference was consistent across all prespecified subgroups (Fig. S3). This difference was also consistent in the subgroup of patients in whom the minimal-function mutation caused an absence of CFTR protein production (78.0% of the trial population) and those with missense or in-frame deletion mutations (Table S3). Patients with a percentage of predicted FEV_1 of less than 40% at baseline (8.4% of the trial population) had a similar magnitude change in percentage of predicted FEV_1 at week 4 as the overall population (Table S4).

Treatment with elexacaftor–tezacaftor–ivacaftor resulted in a 63% lower annualized rate of pulmonary exacerbations than placebo (rate ratio, 0.37; 95% confidence interval, 0.25 to 0.55; P<0.001) (Table 2). A similar benefit was seen with respect to the rate of exacerbations that led to hospitalization or that were treated with intravenous antibiotics (Fig. 1C). A higher percentage of patients in the elexacaftor–tezacaftor–ivacaftor group than in the placebo group remained free of pulmonary exacerbations (Fig. S4).

Sweat chloride concentrations improved significantly through week 24, with a mean treatment difference of −41.8 mmol per liter relative to placebo (P<0.001) (Table 2 and Fig. 2A). The histogram of absolute change in sweat chloride concentration through week 24 showed separation of the two groups (Fig. 2B). The mean sweat chloride concentration in the elexacaftor–tezacaftor–ivacaftor group at week 24 was 57.9 mmol per liter, as compared with 102.4 mmol per liter in the placebo group (Fig. S5).

Table 2. Primary and Key Secondary Efficacy End Points.*

End Point	Elexacaftor–Tezacaftor–Ivacaftor (N=200)	Placebo (N=203)	Difference (95% CI)†	P Value
Primary end point: absolute change in percentage of predicted FEV_1 from baseline at wk 4 (95% CI)‡	13.6 (12.4 to 14.8)	−0.2 (−1.3 to 1.0)	13.8 (12.1 to 15.4)	<0.001
Key secondary end points				
Absolute change in percentage of predicted FEV_1 from baseline through wk 24 (95% CI)	13.9 (12.8 to 15.0)	−0.4 (−1.5 to 0.7)	14.3 (12.7 to 15.8)	<0.001
Pulmonary exacerbations through wk 24 — no. of events (annualized estimated event rate)§	41 (0.37)	113 (0.98)	0.37 (0.25 to 0.55)	<0.001
Absolute change in sweat chloride concentration from baseline through wk 24 (95% CI) — mmol/liter	−42.2 (−44.0 to −40.4)	−0.4 (−2.2 to 1.4)	−41.8 (−44.4 to −39.3)	<0.001
Absolute change in CFQ-R respiratory domain score from baseline through wk 24 (95% CI)¶	17.5 (15.6 to 19.5)	−2.7 (−4.6 to −0.8)	20.2 (17.5 to 23.0)	<0.001
Absolute change in body-mass index from baseline at wk 24 (95% CI)	1.13 (0.99 to 1.26)	0.09 (−0.05 to 0.22)	1.04 (0.85 to 1.23)	<0.001
Absolute change in sweat chloride concentration from baseline at wk 4 (95% CI) — mmol/liter	−41.2 (−43.1 to −39.2)	0.1 (−1.9 to 2.0)	−41.2 (−44.0 to −38.5)	<0.001
Absolute change in CFQ-R respiratory domain score from baseline at wk 4 (95% CI)¶	18.1 (15.9 to 20.4)	−1.9 (−4.2 to 0.3)	20.1 (16.9 to 23.2)	<0.001

* Data are least-squares means with 95% confidence intervals (CIs), except for pulmonary exacerbations through week 24, for which the number of events and the annualized estimated event rate are shown.
† The difference is the least-squares mean difference between the elexacaftor–tezacaftor–ivacaftor group and the placebo group based on a mixed-effects model for repeated measures, except for the number of pulmonary exacerbations, for which the rate ratio is shown.
‡ The primary end point was assessed at the prespecified interim analysis at week 4, which included all patients who underwent randomization and received at least one dose of elexacaftor–tezacaftor–ivacaftor or placebo.
§ The analysis was based on a negative binomial-regression model (48 weeks per year was used to calculate the event rate).
¶ For the CFQ-R respiratory domain score (range, 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms), the minimum clinically important difference is 4 points.

The CFQ-R respiratory domain score improved significantly through week 24 in the elexacaftor–tezacaftor–ivacaftor group, with a mean treatment difference of 20.2 points relative to placebo (P<0.001) (Table 2 and Fig. 2C). BMI also improved significantly at week 24, with a mean treatment difference of 1.04 relative to placebo (P<0.001) (Table 2 and Fig. S6). All additional secondary efficacy end points showed improvement (Table 2 and Table S5).

SAFETY

Table 3 provides an overview of adverse events. The percentage of patients with at least one adverse event was 93.1% in the elexacaftor–tezacaftor–ivacaftor group and 96.0% in the placebo group; excluding adverse events of pulmonary exacerbation, the percentage was 92.6% in the elexacaftor–tezacaftor–ivacaftor group and 93.0% in the placebo group. Adverse events occurring in at least 10% of patients in either trial group were consistent with common manifestations and complications of cystic fibrosis. The majority of patients in the elexacaftor–tezacaftor–ivacaftor group had adverse events that were mild (33.2%) or moderate (50.5%) in severity. The large majority of adverse events resolved during the trial.

Serious adverse events occurred in 28 patients (13.9%) in the elexacaftor–tezacaftor–ivacaftor group and 42 patients (20.9%) in the placebo group (Table 3 and Table S6); excluding serious adverse events of pulmonary exacerbation, serious adverse events occurred in 20 patients (9.9%) in the elexacaftor–tezacaftor–ivacaftor group and 16 patients (8.0%) in the placebo group. There were no deaths in either trial group. Two patients (1.0%) in the elexacaftor–tezacaftor–ivacaftor group discontinued the trial regimen because of adverse events: rash in 1 patient and portal hypertension in a patient with preexisting cirrhosis.

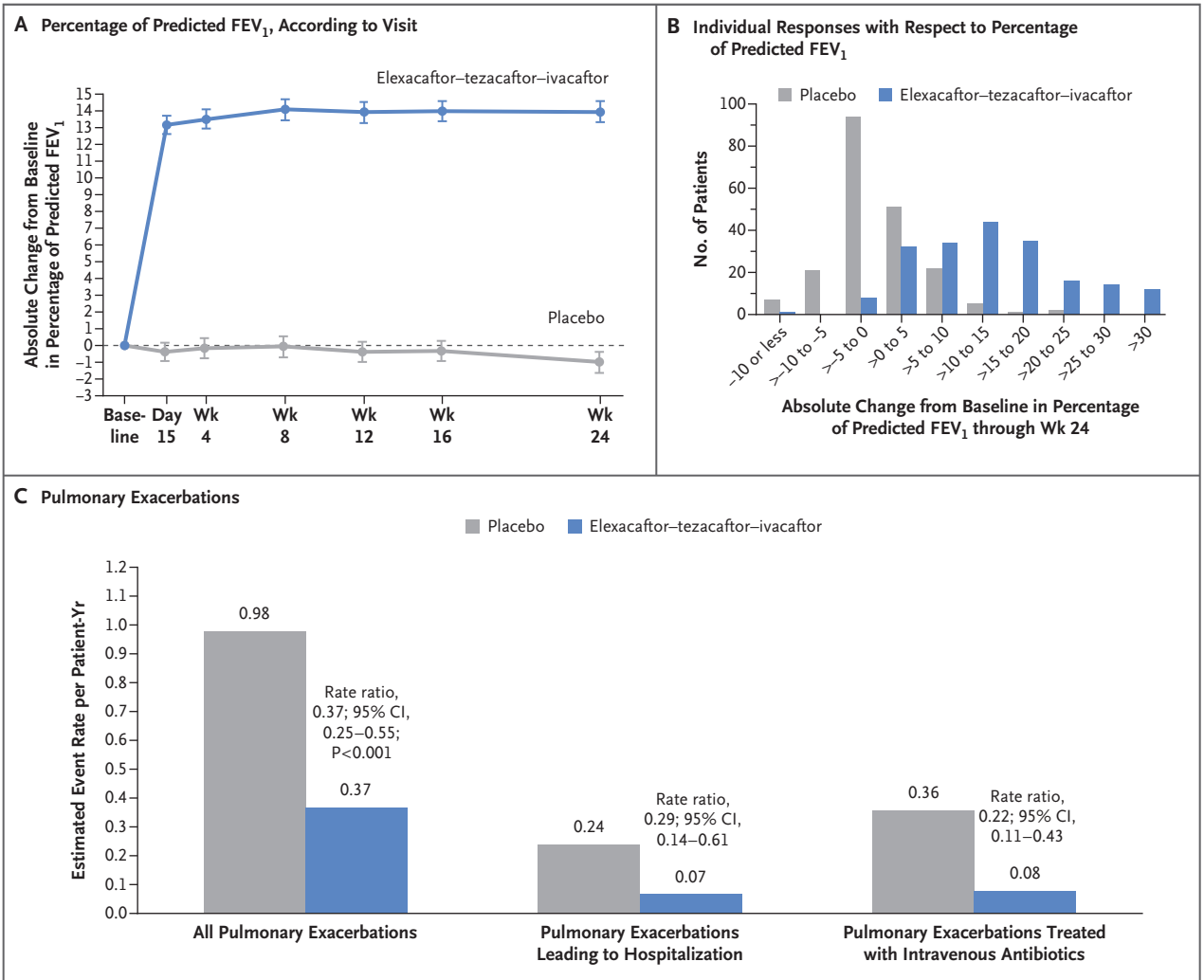

Figure 1. Absolute Change from Baseline in Percentage of Predicted FEV_1, and Rate of Pulmonary Exacerbations.

Panel A shows the absolute change from baseline in percentage of predicted forced expiratory volume in 1 second (FEV_1), based on a mixed-effects model for repeated measures. Data are least-squares means, and I bars indicate standard error of the mean; the dashed line indicates no change from baseline. Panel B shows a histogram of absolute change from baseline in percentage of predicted FEV_1 through week 24, according to trial group. Panel C shows the overall estimated annualized rate of pulmonary exacerbations, the estimated annualized rate of pulmonary exacerbations leading to hospitalization, and the estimated annualized rate of pulmonary exacerbations treated with intravenous antibiotics. CI denotes confidence interval.

No patients in the placebo group discontinued the trial regimen because of an adverse event.

On the basis of previous experience with CFTR modulator therapy,[9-12] including the phase 2 trial of elexacaftor–tezacaftor–ivacaftor,[18] data related to aminotransferase levels and rash were reviewed. Adverse events of elevated aminotransferase levels occurred in 22 patients (10.9%) in the elexacaftor–tezacaftor–ivacaftor group and 8 patients (4.0%) in the placebo group. In the elexacaftor–tezacaftor–ivacaftor group, elevated levels of alanine aminotransferase or aspartate aminotransferase that were greater than three times, greater than five times, and greater than eight times the upper limit of the normal range occurred in 16 patients (7.9%), 5 patients (2.5%), and 3 patients (1.5%), respectively, as compared with 11 patients (5.5%), 3 patients (1.5%), and 2 patients (1.0%) in the placebo group. No patient had an elevated aminotransferase level greater

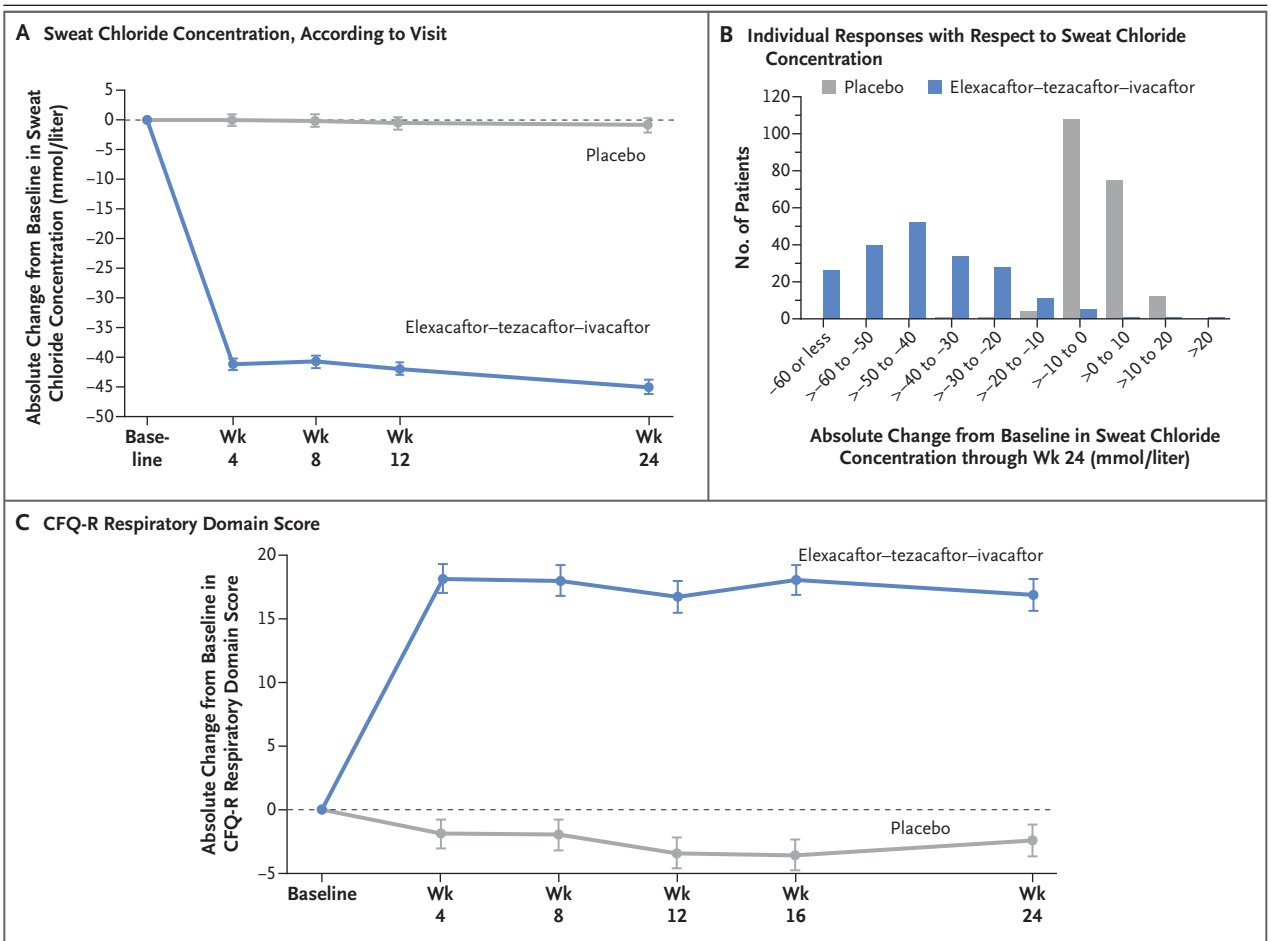

Figure 2. Absolute Change from Baseline in Sweat Chloride Concentration and CFQ-R Respiratory Domain Score.

Panel A shows the absolute change from baseline in sweat chloride concentration, based on a mixed-effects model for repeated measures; a reduction over time indicates improvement in CFTR function. Panel B shows a histogram of absolute change from baseline in sweat chloride concentration through week 24, according to trial group. Panel C shows the absolute change from baseline in the respiratory domain score on the Cystic Fibrosis Questionnaire–Revised (CFQ-R), based on a mixed-effects model for repeated measures. Scores are normalized to range from 0 to 100 points, with higher scores indicating a higher patient-reported quality of life with regard to respiratory symptoms; the minimum clinically important difference is 4 points. In Panels A and C, least-squares means at each visit are shown, and the I bars indicate the corresponding standard error; the dashed line indicates no change from baseline.

than three times the upper limit of the normal range concurrent with an elevated bilirubin level greater than two times the upper limit of the normal range that emerged during the intervention period. Rash occurred in 22 patients (10.9%) in the elexacaftor–tezacaftor–ivacaftor group and 13 patients (6.5%) in the placebo group. In both trial groups, rash was more common in female patients than in male patients and more common in female patients who used hormonal contraceptives than in those who did not (Table S7).

Additional observations included elevated levels of creatine kinase and blood-pressure changes in the elexacaftor–tezacaftor–ivacaftor group. Elevated levels of creatine kinase were often associated with exercise, and no elevations of creatine kinase led to discontinuation of the trial regimen (Table S8). The baseline mean systolic and diastolic blood pressures in the elexacaftor–tezacaftor–ivacaftor group were 113.4 mm Hg and 69.4 mm Hg, and they increased by 3.1 mm Hg and 1.9 mm Hg, respectively, at week 24 (Table S9). There were no relevant safety findings in other clinical or laboratory assessments.

Table 3. Adverse Events.*

Event	Elexacaftor–Tezacaftor–Ivacaftor (N=202)	Placebo (N=201)
	number of patients (percent)	
Any adverse event	188 (93.1)	193 (96.0)
Maximum severity of adverse event		
Mild	67 (33.2)	53 (26.4)
Moderate	102 (50.5)	125 (62.2)
Severe	19 (9.4)	14 (7.0)
Life-threatening	0	1 (0.5)
Serious adverse event	28 (13.9)	42 (20.9)
Adverse event leading to discontinuation of trial regimen	2 (1.0)	0
Adverse event leading to death	0	0
Most common adverse events†		
Infective pulmonary exacerbation of cystic fibrosis	44 (21.8)	95 (47.3)
Sputum increased	40 (19.8)	39 (19.4)
Headache	35 (17.3)	30 (14.9)
Cough	34 (16.8)	77 (38.3)
Diarrhea	26 (12.9)	14 (7.0)
Upper respiratory tract infection	24 (11.9)	22 (10.9)
Nasopharyngitis	22 (10.9)	26 (12.9)
Oropharyngeal pain	20 (9.9)	25 (12.4)
Hemoptysis	11 (5.4)	28 (13.9)
Fatigue	9 (4.5)	20 (10.0)

* Adverse events were coded with the use of the *Medical Dictionary of Regulatory Activities*, version 22.0. A patient with multiple events within a category was counted only once in that category.
† Shown are events that occurred in at least 10% of the patients in either trial group.

DISCUSSION

In this 24-week trial of triple-combination CFTR modulator therapy in patients with cystic fibrosis who have a single Phe508del allele, elexacaftor–tezacaftor–ivacaftor treatment resulted in improvements in lung function, the rate of pulmonary exacerbations, sweat chloride concentration, CFQ-R respiratory domain scores, and BMI and was generally safe with an acceptable side-effect profile, findings that are consistent with those of the phase 2 trial of elexacaftor–tezacaftor–ivacaftor.[18] The efficacy outcomes confirm the hypothesis that elexacaftor–tezacaftor–ivacaftor effectively modulates the function of Phe508del CFTR from a single allele, providing pronounced benefits in a population of patients in whom previous CFTR modulator therapies were not effective.[15,19]

Elexacaftor–tezacaftor–ivacaftor therapy improved multiple outcome measures. FEV_1 is a strong predictor of clinical status in cystic fibrosis,[20] and elexacaftor–tezacaftor–ivacaftor resulted in sustained improvements in this end point. Pulmonary exacerbations are important clinical events associated with disease progression[21-24]; elexacaftor–tezacaftor–ivacaftor resulted in a lower rate of pulmonary exacerbations, including severe events leading to hospitalization or treatment with intravenous antibiotics, than placebo. Improvements in respiratory symptoms and in systemic indicators of clinical benefit, including nutritional outcomes, were also noted.

The current benchmark for highly effective CFTR modulator therapy is ivacaftor for patients with the Gly551Asp *CFTR* mutation,[10] in whom disease modification has been shown with long-term use, including decreased lung-function decline and decreased mortality.[25-28] The improvement in the primary end point of absolute change in percentage of predicted FEV_1 was 10.6 points in patients with the Gly551Asp allele.[10] In the present trial of elexacaftor–tezacaftor–ivacaftor in patients with a single Phe508del allele, the improvement in percentage of predicted FEV_1 was 13.8 points, relative to placebo. Furthermore, the mean sweat chloride concentration in patients with a single Phe508del allele who received elexacaftor–tezacaftor–ivacaftor for 24 weeks decreased from 102 mmol per liter to 58 mmol per liter, just below the generally accepted diagnostic threshold for cystic fibrosis (≥60 mmol per liter)[29]; this finding reflects improved CFTR function.

Ivacaftor and tezacaftor–ivacaftor, two components of this triple combination, are approved therapies, with well-characterized safety profiles.[10-12,30] Similar to these agents, elexacaftor–tezacaftor–ivacaftor therapy was associated with adverse events that were mostly mild to moderate, that generally represented common manifestations of cystic fibrosis, and that led to few treatment discontinuations. An increase in the incidence of elevated aminotransferase levels, which occur sporadically in many persons with

cystic fibrosis, was observed with elexacaftor–tezacaftor–ivacaftor treatment; these adverse events were low grade (i.e., mild or moderate) in 20 of 22 patients (91%) and were not treatment-limiting. In general, cases of rash were mild to moderate and did not lead to alteration of treatment administration. The elevated serum levels of creatine kinase that were observed were generally asymptomatic and often associated with exercise. The modest increase in mean blood pressure that was observed with elexacaftor–tezacaftor–ivacaftor may be related to salt preservation,[31] improved nutritional status, or other effects of CFTR modulation; evaluation of blood pressure in patients who begin to receive treatment may help to clarify the clinical relevance of this observation.

Unlike previous CFTR modulators, triple-combination therapy with elexacaftor–tezacaftor–ivacaftor strongly modulates CFTR in persons with Phe508del–minimal function genotypes. The effect on Phe508del CFTR was evident in the 78% of patients with minimal-function mutations that are associated with an absence of CFTR protein production, who had a response to elexacaftor–tezacaftor–ivacaftor that could occur only through modulation of Phe508del CFTR. These data support the hypothesis that the presence of a single Phe508del allele is sufficient to impart the benefit of triple-combination therapy independent of the minimal-function mutation. The restoration of Phe508del CFTR by elexacaftor–tezacaftor–ivacaftor was further confirmed by a concurrent phase 3 trial involving patients with two Phe508del alleles, which showed substantially improved outcomes, including increased lung function and decreased patient-reported respiratory symptoms, as compared with the dual combination of tezacaftor–ivacaftor.[32] Further research to extend the benefit of CFTR modulation to patients with responsive mutations other than the Phe508del *CFTR* mutation is imperative.

In conclusion, this 24-week, phase 3 trial involving 403 patients with cystic fibrosis confirmed the efficacy of triple-combination CFTR modulator therapy in patients 12 years of age or older who were heterozygous for the Phe508del *CFTR* mutation and a minimal-function mutation. No worrisome safety signals were noted. These results provide evidence that elexacaftor–tezacaftor–ivacaftor can modulate a single Phe508del allele in people with cystic fibrosis, thus addressing the underlying cause of disease in the large majority of patients.

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APPENDIX

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