Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del

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Abstract: BACKGROUND: Combination treatment with the cystic fibrosis transmembrane conductance regulator (CFTR) modulators tezacaftor (VX-661) and ivacaftor (VX-770) was designed to target the underlying cause of disease in patients with cystic fibrosis. METHODS: In this phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial, we evaluated combination therapy with tezacaftor and ivacaftor in patients 12 years of age or older who had cystic fibrosis and were homozygous for the CFTR Phe508del mutation. Patients were randomly assigned in a 1:1 ratio to receive either 100 mg of tezacaftor once daily and 150 mg of ivacaftor twice daily or matched placebo for 24 weeks. The primary end point was the absolute change in the percentage of the predicted forced expiratory volume in 1 second (FEV1) through week 24 (calculated in percentage points); relative change in the percentage of the predicted FEV1 through week 24 (calculated as a percentage) was a key secondary end point. RESULTS: Of the 510 patients who underwent randomization, 509 received tezacaftor-ivacaftor or placebo, and 475 completed 24 weeks of the trial regimen. The mean FEV1 at baseline was 60.0% of the predicted value. The effects on the absolute and relative changes in the percentage of the predicted FEV1 in favor of tezacaftor-ivacaftor over placebo were 4.0 percentage points and 6.8%, respectively ($P<0.001$ for both comparisons). The rate of pulmonary exacerbation was 35% lower in the tezacaftor-ivacaftor group than in the placebo group ($P=0.005$). The incidence of adverse events was similar in the two groups. Most adverse events were of mild severity (in 41.8% of patients overall) or moderate severity (in 40.9% overall), and serious adverse events were less frequent with tezacaftor-ivacaftor (12.4%) than with placebo (18.2%). A total of 2.9% of patients discontinued the assigned regimen owing to adverse events. Fewer patients in the tezacaftor-ivacaftor group than in the placebo group had respiratory adverse events, none of which led to discontinuation. CONCLUSIONS: The combination of tezacaftor and ivacaftor was efficacious and safe in patients 12 years of age or older who had cystic fibrosis and were homozygous for the CFTR Phe508del mutation. (Funded by Vertex Pharmaceuticals; EVOLVE ClinicalTrials.gov number, NCT02347657 .).

DOI: https://doi.org/10.1056/NEJMoa1709846

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DOI: https://doi.org/10.1056/NEJMoa1709846

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 23, 2017 VOL. 377 NO. 21

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ABSTRACT

BACKGROUND

Combination treatment with the cystic fibrosis transmembrane conductance regulator (CFTR) modulators tezacaftor (VX-661) and ivacaftor (VX-770) was designed to target the underlying cause of disease in patients with cystic fibrosis.

METHODS

In this phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial, we evaluated combination therapy with tezacaftor and ivacaftor in patients 12 years of age or older who had cystic fibrosis and were homozygous for the *CFTR* Phe508del mutation. Patients were randomly assigned in a 1:1 ratio to receive either 100 mg of tezacaftor once daily and 150 mg of ivacaftor twice daily or matched placebo for 24 weeks. The primary end point was the absolute change in the percentage of the predicted forced expiratory volume in 1 second (FEV_1) through week 24 (calculated in percentage points); relative change in the percentage of the predicted FEV_1 through week 24 (calculated as a percentage) was a key secondary end point.

RESULTS

Of the 510 patients who underwent randomization, 509 received tezacaftor–ivacaftor or placebo, and 475 completed 24 weeks of the trial regimen. The mean FEV_1 at baseline was 60.0% of the predicted value. The effects on the absolute and relative changes in the percentage of the predicted FEV_1 in favor of tezacaftor–ivacaftor over placebo were 4.0 percentage points and 6.8%, respectively ($P<0.001$ for both comparisons). The rate of pulmonary exacerbation was 35% lower in the tezacaftor–ivacaftor group than in the placebo group ($P=0.005$). The incidence of adverse events was similar in the two groups. Most adverse events were of mild severity (in 41.8% of patients overall) or moderate severity (in 40.9% overall), and serious adverse events were less frequent with tezacaftor–ivacaftor (12.4%) than with placebo (18.2%). A total of 2.9% of patients discontinued the assigned regimen owing to adverse events. Fewer patients in the tezacaftor–ivacaftor group than in the placebo group had respiratory adverse events, none of which led to discontinuation.

CONCLUSIONS

The combination of tezacaftor and ivacaftor was efficacious and safe in patients 12 years of age or older who had cystic fibrosis and were homozygous for the *CFTR* Phe508del mutation. (Funded by Vertex Pharmaceuticals; EVOLVE ClinicalTrials.gov number, NCT02347657.)

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A complete list of investigators in the EVOLVE trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 3, 2017, at NEJM.org.

N Engl J Med 2017;377:2013-23.
DOI: 10.1056/NEJMoa1709846

Cystic fibrosis is caused by a reduced quantity or function of cystic fibrosis transmembrane conductance regulator (CFTR) protein, owing to mutations in *CFTR*. A loss of chloride secretion causes impaction of mucus in the airways, gastrointestinal tract, and exocrine organs, with important clinical consequences that include progressive loss of lung function, nutritional deficits, pulmonary exacerbations, and respiratory failure.[1,2] Cystic fibrosis affects more than 80,000 persons worldwide. Phe508del is the most prevalent *CFTR* mutation worldwide; approximately 46% of patients with cystic fibrosis in the United States are homozygous for this allele, as are 49% of those in Canada and 40% of those in Europe.[3-6] The Phe508del mutation leads to greatly reduced CFTR protein activity owing to impaired processing and trafficking of CFTR to the epithelial-cell surface, as well as impaired function of the small quantity of the protein that is produced and trafficked to epithelial membranes.[7-9]

CFTR modulators are a family of new compounds that target specific defects caused by mutations in *CFTR* and thereby treat the underlying cause of cystic fibrosis. Ivacaftor, a CFTR potentiator and the first approved CFTR modulator, increases the probability of channel opening (i.e., the fraction of time that the channels are open) of normal and mutant CFTR protein in vitro.[10] The drug has been approved for use in patients with a broad range of *CFTR* gating and other mutations that produce some CFTR protein on the epithelial-cell surface.[11-16] In long-term registry studies, ivacaftor has reduced mortality and rates of lung transplantation and other complications of cystic fibrosis among patients with gating mutations.[17] Lumacaftor, a CFTR corrector, improves processing and trafficking of CFTR protein[18] and, in combination with ivacaftor, is approved for use in patients who are homozygous for the Phe508del *CFTR* mutation on the basis of randomized clinical trials that have shown improved lung function and nutritional status and a reduced frequency of exacerbations.[19-22]

Ivacaftor and the combination therapy lumacaftor–ivacaftor have both been associated with a rate of progressive decline in lung function that is lower than the rate observed among untreated, matched, control registry patients, which shows that effective CFTR modulators may modify the course of disease.[19,23] However, not all patients who are homozygous for the Phe508del mutation can receive lumacaftor–ivacaftor because of its respiratory side-effect profile.[24-26] In addition, strong cytochrome P-450-3A induction by lumacaftor causes prohibitive drug–drug interactions in some patients and limits the use of lumacaftor–ivacaftor in patients with ivacaftor-responsive mutations.[27] Therefore, new CFTR modulator treatments for the population of patients who are homozygous for the Phe508del mutation are needed.

Tezacaftor is an investigational CFTR corrector that, in combination with ivacaftor, has shown efficacy in preclinical studies[28] and has shown enhanced CFTR function and improved lung function in a phase 2 clinical trial involving patients who were homozygous for the Phe508del mutation or heterozygous for the Phe508del and G551D mutations.[29] Here, we report the findings of a phase 3 trial that evaluated the efficacy and safety of tezacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the Phe508del mutation.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial (VX14-661-106, also called EVOLVE) involved patients 12 years of age or older with cystic fibrosis who were homozygous for the Phe508del *CFTR* mutation. The trial was conducted at 91 sites in the United States, Canada, and Europe from January 30, 2015, to January 20, 2017. Combination therapy with tezacaftor and ivacaftor (VX-661 and VX-770, respectively; Vertex Pharmaceuticals) or placebo was administered for 24 weeks. The primary objective was to evaluate the efficacy of tezacaftor–ivacaftor as compared with placebo, and the safety of tezacaftor–ivacaftor was a secondary objective. The trial protocol (available with the full text of this article at NEJM.org) and informed-consent forms were approved by an independent ethics committee or institutional review board for each trial site. All the enrolled patients, or their parent or legal guardian, provided written informed consent; when appropriate, assent was obtained from the patients. Safety was monitored by an independent data and safety monitoring committee that comprised members of the Cystic Fibrosis Foundation Data Safety Monitoring Board.

Patients were randomly assigned in a 1:1 ratio to receive either a combination of 100 mg of tezacaftor once daily and 150 mg of ivacaftor twice daily (administered as a fixed-dose combination tablet containing 100 mg of tezacaftor and 150 mg of ivacaftor in the morning and a tablet containing 150 mg of ivacaftor in the evening) or matched placebo for 24 weeks. The tezacaftor–ivacaftor dose regimen was selected on the basis of the results of a phase 2 dose-escalation study.[29] Randomization was stratified according to age (<18 years vs. ≥18 years), sex, and the percentage of the predicted forced expiratory volume in 1 second (FEV_1) (<70% vs. ≥70%) at screening. At trial completion, patients were given the option to enroll in a 96-week open-label extension study (VX14-661-110; ClinicalTrials.gov number, NCT02565914); patients began the extension study immediately after completion of the 24-week trial.

The trial sponsor (Vertex Pharmaceuticals) designed the protocol in collaboration with the authors. Data were collected by local site investigators (see the Supplementary Appendix, available at NEJM.org) and analyzed by the sponsor. All the authors had full access to the trial data after the data were unblinded. The manuscript was written with the assistance of medical writers, with funding by the sponsor; all the authors provided critical review and input. Final decisions regarding the content of the submitted manuscript were made by the first and last authors. All the authors made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Confidentiality agreements were in place between the sponsor and all the investigators participating in the trial.

TRIAL PARTICIPANTS

Patients 12 years of age or older who had a confirmed diagnosis of cystic fibrosis and two Phe508del alleles, a percentage of the predicted FEV_1 between 40% and 90% at screening, and stable disease, as judged by the investigator, were eligible for inclusion. The full inclusion and exclusion criteria are provided in the Supplementary Appendix. At screening, all the patients underwent *CFTR* genotype confirmation. Values for the percentage of predicted FEV_1 that were outside the range of 40 to 90% were permitted at baseline.

ASSESSMENTS

The primary end point was the absolute change in the percentage of the predicted FEV_1 from baseline through week 24, including assessments at day 15 and weeks 4, 8, 12, 16, and 24. Key secondary end points were the relative change in the percentage of the predicted FEV_1 from baseline through week 24, the number of pulmonary exacerbations through week 24, the absolute change from baseline in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) at the week 24 visit, and the absolute change in the respiratory domain score on the Cystic Fibrosis Questionnaire–Revised (CFQ-R; scores are on a scale from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status) from baseline through week 24. Further details regarding the calculation of the absolute and relative changes in the percentages of the predicted FEV_1 are provided in the Supplementary Appendix.

The safety assessment was based on adverse events, clinical laboratory values, electrocardiograms, vital signs, pulse oximetry, and spirometry. The time to the first pulmonary exacerbation, the absolute change in the sweat chloride concentration (an in vivo marker of CFTR function) from baseline through week 24, and the absolute change from baseline in the BMI-for-age z score at the week 24 visit (in patients <20 years of age at screening) were also assessed as secondary end points. Assessments were carried out at all trial visits (except for the assessments of the sweat chloride concentration and CFQ-R score), including a safety follow-up visit that occurred 4 weeks (within a window of ±7 days) after the receipt of the last dose of tezacaftor–ivacaftor or placebo in patients who elected not to enroll in the extension study (see the Study Assessments section and Fig. S1 in the Supplementary Appendix).

STATISTICAL ANALYSIS

Efficacy analyses included all the patients who had undergone randomization, who had received at least one dose of tezacaftor–ivacaftor or placebo, and who were homozygous for the Phe508del mutation. The primary analysis — the evaluation of the difference in the absolute change from baseline in the percentage of the predicted FEV_1 through week 24 between the tezacaftor–ivacaftor

group and the placebo group — was based on a mixed-effects model for repeated measures. The percentage of the predicted FEV_1 was calculated with the use of the standards of Wang et al.[30] (for female patients 12 to 15 years of age and male patients 12 to 17 years of age) or Hankinson et al.[31] (for female patients ≥16 years of age and male patients ≥18 years of age). The standard that was used for individual patients was changed from that of Wang et al. to that of Hankinson et al. if they had a birthday during the trial that moved them from the younger age group to the older age group.

The key secondary efficacy end points, which were measured at scheduled time points through week 24, were analyzed by means of a mixed-effects model for repeated measures and (for the number of pulmonary exacerbations) a negative binomial regression analysis. A fixed-sequence hierarchical testing procedure was used to control the overall type I error at a level of 0.05 for the multiple hypothesis tests, including the primary and key secondary efficacy end points (see the Methods section in the Supplementary Appendix). The time to the first pulmonary exacerbation was compared between the trial groups as a secondary end point with the use of a Cox regression model that included trial group, sex, age at screening (<18 years vs. ≥18 years), and the baseline percentage of the predicted FEV_1 as covariates. Safety analyses included all the patients who had received at least one dose of tezacaftor–ivacaftor or placebo, including those with ineligible genotypes; these analyses were based on data from the period from the first dose of trial regimen to the earliest of the following: the safety follow-up visit, 28 days after last dose of trial regimen for patients who did not have a safety follow-up visit, or the day immediately before the first dose received in the VX14-661-110 extension study for patients who enrolled in that study.

RESULTS

POPULATION OF PATIENTS

A total of 510 patients were enrolled and underwent randomization; 509 patients received at least one dose of tezacaftor–ivacaftor (251 patients) or placebo (258 patients) (Fig. S2 in the Supplementary Appendix). One patient who had been randomly assigned to the placebo group did not receive any placebo because of a pulmonary exacerbation before the day 1 visit. Five patients underwent randomization (3 patients to the tezacaftor–ivacaftor group and 2 to the placebo group) and received the assigned trial regimen but had an ineligible or unconfirmed *CFTR* genotype so were excluded from the efficacy analyses but not the safety analyses. Overall, 475 patients (235 [93.6%] in the tezacaftor–ivacaftor group and 240 [93.0%] in the placebo group) completed 24 weeks of the trial. A total of 15 patients (2.9%) discontinued owing to adverse events (7 [2.8%] patients in the tezacaftor–ivacaftor group and 8 [3.1%] in the placebo group). Sex, age, concomitant medication use, geographic region (North America vs. Europe), *Pseudomonas aeruginosa* infection, and percentage of the predicted FEV_1 were well balanced between the two groups (Table 1, and Table S1 in the Supplementary Appendix). The overall mean (±SD) percentage of the predicted FEV_1 in the trial population was 60.0±15.2%. A total of 461 patients (90.6% of those who received at least one dose of tezacaftor–ivacaftor or placebo) enrolled in the treatment cohort of the open-label extension study, including 231 patients who had been in the tezacaftor–ivacaftor group and 230 who had been in the placebo group.

CLINICAL EFFICACY

A total of 504 patients (248 in the tezacaftor–ivacaftor group and 256 in the placebo group) were included in the efficacy analyses. The use of tezacaftor–ivacaftor led to a significantly greater absolute change from baseline in the percentage of the predicted FEV_1 than placebo (least-squares mean difference through 24 weeks, 4.0 percentage points; 95% confidence interval [CI], 3.1 to 4.8; P<0.001) (Table 2). The mean absolute change from baseline through week 24 was 3.4 percentage points in the tezacaftor–ivacaftor group, as compared with −0.6 percentage points in the placebo group. In the tezacaftor–ivacaftor group, an increased percentage of the predicted FEV_1 was observed at the first assessment (on day 15) and was maintained at all trial visits through week 24 (Fig. 1). The difference was consistent across all the prespecified subgroup analyses (Fig. S3 in the Supplementary Appendix). The least-squares mean difference between groups in the relative change from baseline in the percentage of the predicted FEV_1 through week 24 was 6.8% (95% CI, 5.3 to 8.3; P<0.001) (Table 2). Absolute and relative changes in FEV_1 from baseline through

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Placebo Group (N=256)	Tezacaftor–Ivacaftor Group (N=248)
Female sex — no. (%)	125 (48.8)	121 (48.8)
Age at screening		
Mean — yr	25.7±9.5	26.9±11.2
Distribution — no. (%)		
<18 yr	58 (22.7)	58 (23.4)
≥18 yr	198 (77.3)	190 (76.6)
Geographic region — no. (%)		
North America	68 (26.6)	59 (23.8)
Europe	188 (73.4)	189 (76.2)
Percentage of predicted FEV_1		
Mean value	60.4±15.7	59.6±14.7
Distribution — no. (%)		
<40%	24 (9.4)	23 (9.3)
≥40% to <70%	152 (59.4)	157 (63.3)
≥70% to ≤90%	73 (28.5)	65 (26.2)
>90%	7 (2.7)	2 (0.8)
Missing data	0	1 (0.4)
Body-mass index†	21.12±2.88	20.96±2.95
Sweat chloride — mmol/liter	100.5±10.2	101.3±10.9
CFQ-R respiratory domain score‡	69.9±16.6	70.1±16.8
Pseudomonas aeruginosa–positive — no. (%)	182 (71.1)	185 (74.6)

* Plus–minus values are means ±SD. There were no significant between-group differences in any of these characteristics. FEV_1 denotes forced expiratory volume in 1 second.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Cystic Fibrosis Questionnaire–Revised (CFQ-R) range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status.

week 24 are shown in Table S2 in the Supplementary Appendix.

Patients who received tezacaftor–ivacaftor had an annualized estimated event rate of pulmonary exacerbations that was significantly lower than the rate among those who received placebo (0.64 vs. 0.99 events per year; rate ratio, 0.65 [representing a 35% lower rate]; 95% CI, 0.48 to 0.88; P=0.005) (Table 2). The rate of pulmonary exacerbations that led to hospitalization or treatment with intravenous antibiotic agents (or both) was also lower in the tezacaftor–ivacaftor group than in the placebo group (0.29 vs. 0.54 events per year; rate ratio, 0.53; 95% CI, 0.34 to 0.82). The risk of pulmonary exacerbation at 24 weeks was 35% in the placebo group and 25% in the tezacaftor–ivacaftor group, and on the basis of the Cox regression model, the hazard ratio for pulmonary exacerbation in the tezacaftor–ivacaftor group, as compared with the placebo group, was 0.64 (95% CI, 0.46 to 0.88) (Fig. 2A).

No significant difference in the BMI at week 24 was noted between the tezacaftor–ivacaftor group and the placebo group (Table 2 and Fig. 2B). Therefore, the testing hierarchy for statistical significance was broken at this end point. The mean BMI was increased from baseline in both the tezacaftor–ivacaftor group and the placebo group at week 24 (least-squares mean increase, 0.18 [95% CI, 0.08 to 0.28] and 0.12 [95% CI, 0.03 to 0.22], respectively).

The least-squares mean difference between groups in the CFQ-R respiratory domain score through week 24 was 5.1 points (95% CI, 3.2 to 7.0), favoring tezacaftor–ivacaftor (Table 2 and Fig. 2C). In an additional analysis, the percent-

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Placebo Group (N = 256)	Tezacaftor–Ivacaftor Group (N = 248)	Difference (95% CI)	P Value
Primary end point				
Absolute change from baseline in percentage of predicted FEV_1 through wk 24 (95% CI) — percentage points	–0.6 (–1.3 to 0.0)	3.4 (2.7 to 4.0)	4.0 (3.1 to 4.8)	<0.001
Key secondary end points				
Relative change from baseline in percentage of predicted FEV_1 through wk 24 (95% CI) — %	–0.5 (–1.7 to 0.6)	6.3 (5.1 to 7.4)	6.8 (5.3 to 8.3)	<0.001
Pulmonary exacerbation through wk 24 — no. of events (annualized estimated event rate)	122 (0.99)	78 (0.64)	0.65 (0.48 to 0.88)†	0.005
Absolute change from baseline in BMI at wk 24 (95% CI)	0.12 (0.03 to 0.22)	0.18 (0.08 to 0.28)	0.06 (–0.08 to 0.19)	0.41
Absolute change from baseline in CFQ-R respiratory domain score through wk 24 (95% CI)	–0.1 (–1.6 to 1.4)	5.0 (3.5 to 6.5)	5.1 (3.2 to 7.0)	—
Other secondary end points				
Absolute change from baseline in BMI-for-age z score from baseline at wk 24 (95% CI)‡	–0.02 (–0.10 to 0.06)	–0.06 (–0.14 to 0.02)	–0.04 (–0.15 to 0.07)	—
Absolute change from baseline in sweat chloride concentration through wk 24 (95% CI) — mmol/liter	0.2 (–0.8 to 1.2)	–9.9 (–10.9 to –8.9)	–10.1 (–11.4 to –8.8)	—

* Data are least-squares means with 95% confidence intervals, except for the number of patients with 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 tezacaftor–ivacaftor group and the placebo group on the basis of the mixed-effects model for repeated measures, except for the number of pulmonary exacerbations, for which the rate ratio is shown. P values are for the between-group comparisons in all cases. P values are provided for the comparisons listed until the testing hierarchy for statistical significance broke. BMI denotes body-mass index.

† The between-group difference is expressed as a rate ratio. The analysis was based on a negative binomial regression model (48 weeks per year was used to calculate the event rate).

‡ Data included only patients who were younger than 20 years of age at baseline (76 patients in the placebo group and 80 in the tezacaftor–ivacaftor group).

age of patients who had an increase in the CFQ-R respiratory domain score of at least 4 points (i.e., the minimal important difference in this age group[32]) was greater in the tezacaftor–ivacaftor group than in the placebo group (51.1% vs. 35.7%; odds ratio, 2.17; 95% CI, 1.47 to 3.21). The use of tezacaftor–ivacaftor resulted in a reduction (indicating improvement in CFTR function) in the sweat chloride concentration, with a between-group difference of –10.1 mmol per liter (95% CI, –11.4 to –8.8) (Table 2 and Fig. 2D).

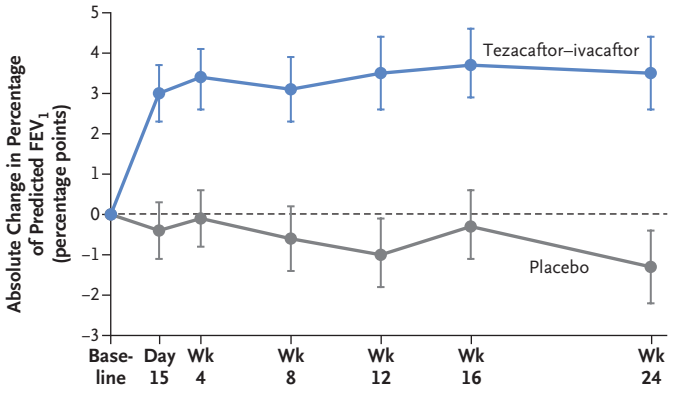

Figure 1. Absolute Change from Baseline in the Percentage of the Predicted Forced Expiratory Volume in 1 Second (FEV_1).

Data are least-squares means, and I bars indicate 95% confidence intervals. The dashed line indicates no change from baseline.

SAFETY

A total of 472 of 509 patients (92.7%) reported having at least one adverse event, including 90.4% of the patients in the tezacaftor–ivacaftor group and 95.0% of those in the placebo group. Most events were of mild severity (in 41.8% of patients overall) or moderate severity (in 40.9%), and there were few grade 3 or 4 events (Table 3). The safety profile of tezacaftor–ivacaftor was consistent across subgroups that were defined according to age, sex, baseline percentage of the predicted FEV_1, and geographic region (Table S3 in the Supplementary Appendix). Serious adverse events were reported in 31 patients (12.4%) in the tezacaftor–ivacaftor group and in 47 (18.2%) in the placebo group (Table S4 in the Supplementary Appendix).

No deaths occurred during the trial. Seven patients (2.8%) in the tezacaftor–ivacaftor group and eight (3.1%) in the placebo group discontinued the trial regimen owing to adverse events. Adverse events interrupted the trial regimen in two patients (0.8%) in the tezacaftor–ivacaftor group and in eight (3.1%) in the placebo group (Table S5 in the Supplementary Appendix).

The most commonly observed adverse events (>10% incidence in either trial group) were infective pulmonary exacerbation, cough, headache, nasopharyngitis, increased sputum production, pyrexia, hemoptysis, oropharyngeal pain, and fatigue. The commonly observed adverse events occurred more frequently in the placebo group than in the tezacaftor–ivacaftor group (Table 3; adverse events with an incidence of ≥5% in either group are shown in Table S6 in the Supplementary Appendix). Adverse events with both an incidence of at least 5% in either group and an incidence that was at least 1 percentage point higher in the tezacaftor–ivacaftor group than in the placebo group were headache, nausea, and nasopharyngitis. Fewer patients in the tezacaftor–ivacaftor group than in the placebo group had prespecified respiratory events of special interest (33 patients [13.1%]) vs. 41 patients [15.9%]), a trend that was consistent across subgroups defined according to the baseline percentage of the predicted FEV_1 (Tables S7 and S8 in the Supplementary Appendix). There were no discontinuations of the trial regimen that were due to respiratory events. The incidence of respiratory events was not greater at the initiation of tezacaftor–ivacaftor than at the initiation of placebo. In the subgroup of patients younger than 18 years of age at screening, no acute bronchoconstriction or decline in the mean postdose FEV_1 was noted at 2 hours or 4 hours after the administration of tezacaftor–ivacaftor (Table S9 in the Supplementary Appendix).

The incidence of abnormal findings on liver-function tests was low and similar in the two groups (Table S10 in the Supplementary Appendix). No major differences in electrocardiogram findings, results on pulse oximetry, or vital signs were observed between the groups.

DISCUSSION

In this phase 3 trial involving patients with cystic fibrosis who were homozygous for the Phe508del mutation, tezacaftor–ivacaftor resulted in significant improvements in lung function that were consistent in all the prespecified subgroups. Tezacaftor–ivacaftor also resulted in a significantly lower rate of pulmonary exacerbations than pla-

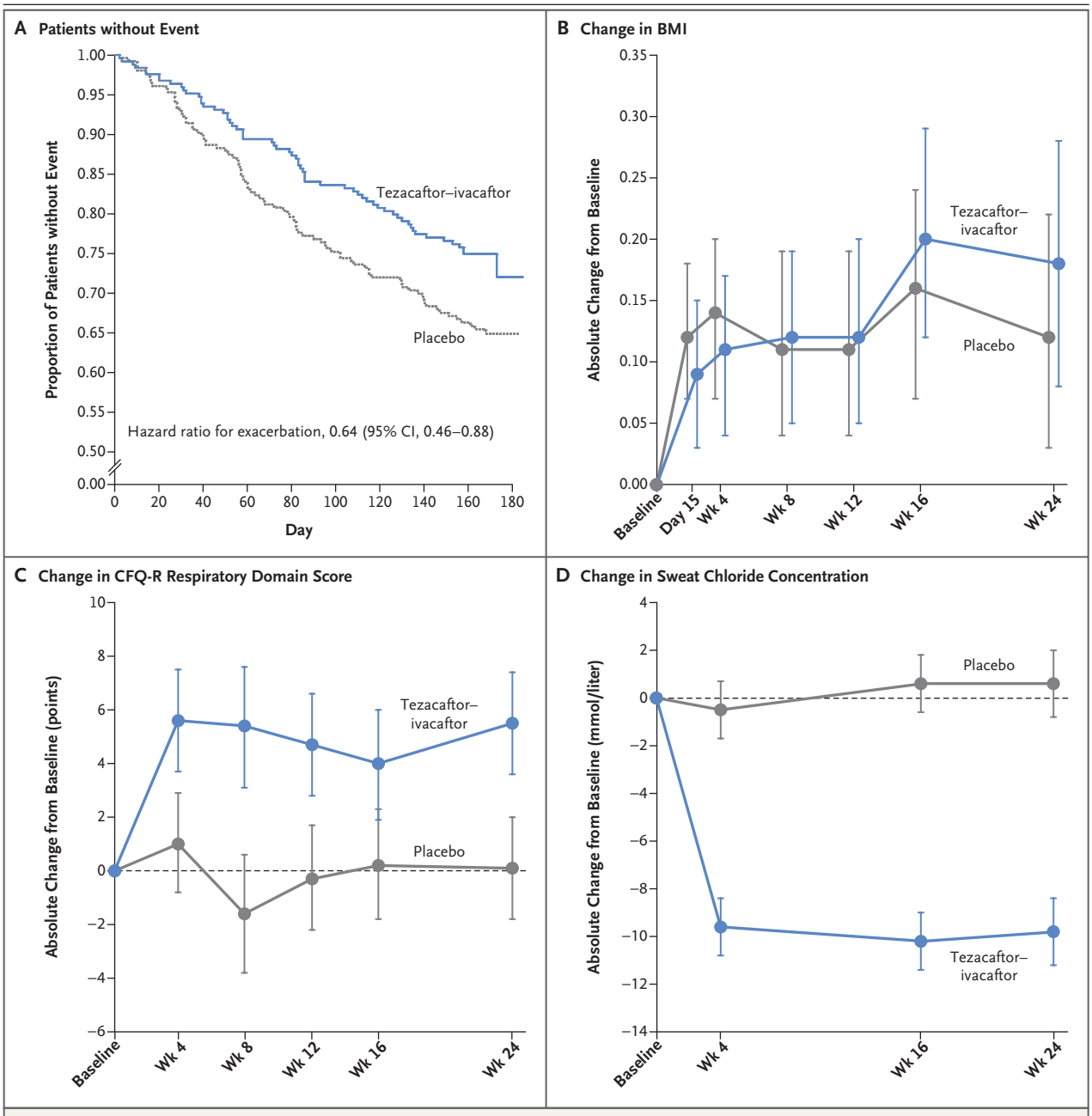

Figure 2. Proportion of Patients Free from Exacerbation Events and Changes in Body-Mass Index (BMI), Cystic Fibrosis Questionnaire–Revised (CFQ-R) Respiratory Domain Score, and Sweat Chloride Concentration.

Panel A shows the proportion of patients who were free from events of pulmonary exacerbation. Panel B shows the absolute changes from baseline in the BMI (the weight in kilograms divided by the square of the height in meters). Panel C shows the absolute change from baseline in the respiratory domain score on the CFQ-R; scores range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status. Panel D shows the sweat chloride concentration; a reduction indicates improvement in CFTR function. The data in Panels B, C, and D are least-squares means, and I bars indicate 95% confidence intervals; the dashed line in Panels C and D indicates no change from baseline.

Table 3. Adverse Events.

Event	Placebo Group (N = 258)	Tezacaftor–Ivacaftor Group (N = 251)
	number of patients (percent)	
Any adverse event	245 (95.0)	227 (90.4)
Adverse event related to trial regimen*	66 (25.6)	64 (25.5)
Adverse event, according to maximum severity		
Mild	99 (38.4)	114 (45.4)
Moderate	117 (45.3)	91 (36.3)
Severe	29 (11.2)	21 (8.4)
Life-threatening†	0	1 (0.4)
Grade 3 or 4 adverse event	29 (11.2)	22 (8.8)
Serious adverse event	47 (18.2)	31 (12.4)
Serious adverse event related to the trial regimen*	3 (1.2)	5 (2.0)
Adverse event leading to discontinuation	8 (3.1)	7 (2.8)
Adverse event leading to death	0	0
Most common adverse event‡		
Infective pulmonary exacerbation of cystic fibrosis	96 (37.2)	75 (29.9)
Cough	84 (32.6)	66 (26.3)
Headache	37 (14.3)	44 (17.5)
Nasopharyngitis	39 (15.1)	42 (16.7)
Increased sputum production	42 (16.3)	36 (14.3)
Pyrexia	32 (12.4)	28 (11.2)
Hemoptysis	35 (13.6)	26 (10.4)
Oropharyngeal pain	29 (11.2)	22 (8.8)
Fatigue	31 (12.0)	16 (6.4)

* The determination of relatedness to the trial regimen was made by the investigators.
† One patient in the tezacaftor–ivacaftor group had a life-threatening serious adverse event of hemoptysis.
‡ The most common adverse events were those that occurred in more than 10% of the patients in either trial group.

cebo. The use of tezacaftor–ivacaftor was associated with a low rate of discontinuation due to adverse events, and no new risks attributable to tezacaftor–ivacaftor were identified. The rate of respiratory adverse events was not higher in the tezacaftor–ivacaftor group than in the placebo group, which shows that the safety profile for tezacaftor–ivacaftor is better than that reported for lumacaftor–ivacaftor.

Despite advances in standard-of-care therapy, patients with cystic fibrosis continue to lose lung function at a rate of approximately 1 to 3% per year.[33] The majority of patients with cystic fibrosis die from their lung disease,[5] and the median predicted survival is 39 years.[34] This trial showed a significant effect of tezacaftor–ivacaftor versus placebo in the absolute change from baseline in the percentage of the predicted FEV_1 through 24 weeks, the primary end point of the trial. This effect was rapid in onset, was sustained throughout the trial, and was observed in all the prespecified subgroups.

Tezacaftor–ivacaftor was associated with a significantly lower frequency of pulmonary exacerbations than placebo, as well as a longer time to the first exacerbation and a lower rate of ex-

acerbations that led to hospitalization or the use of intravenous antibiotics. Pulmonary exacerbations in patients with cystic fibrosis are associated with an accelerated decline in lung function, a worsening quality of life, an increased health care burden, and early death,[35-38] and a reduction in the frequency of exacerbations is therefore a key goal of therapy.

No significant effect on BMI (or on BMI-for-age z scores) was observed at week 24. This finding is in contrast to the increase in BMI that was seen in studies of ivacaftor involving children and adults and in one of the two pivotal studies of lumacaftor–ivacaftor.[11,14,21] However, modest increases in BMI were observed in both the tezacaftor–ivacaftor group and the placebo group in the present trial. The mean BMI in the two trial groups was in the normal healthy range[39] (18.5 to 25.0) at baseline, and patients were encouraged (per the trial protocol) to follow the standard high-fat diet during the trial period. These factors may have obscured the effects of tezacaftor–ivacaftor on nutritional outcomes. The use of tezacaftor–ivacaftor led to an improvement in the respiratory domain scores on the CFQ-R (assessed after the testing hierarchy was broken), including assessments of cough, sputum production, and difficulty breathing — findings that indicate that tezacaftor–ivacaftor resulted in improved quality of life in these patients. In addition, the use of tezacaftor–ivacaftor led to a rapid and sustained reduction (indicating improvement) in the sweat chloride concentration, a pharmacodynamic marker of CFTR function.

The incidence of adverse events was similar in the tezacaftor–ivacaftor group and the placebo group. Adverse events led to the discontinuation of the trial regimen in few patients, and no new safety signals were seen. In contrast to treatment with lumacaftor–ivacaftor in phase 3 and phase 4 trials,[19,21,24-26] tezacaftor–ivacaftor was not associated with an increased incidence of respiratory events or an acute postdose decline in the percentage of the predicted FEV_1.

In conclusion, this 24-week trial showed the efficacy and safety of tezacaftor–ivacaftor in patients 12 years of age or older who had cystic fibrosis and were homozygous for the *CFTR* Phe508del mutation. The improved safety profile of combination therapy with tezacaftor–ivacaftor, as compared with currently available therapy, in addition to its effect on multiple efficacy end points, supports its use in a broad range of patients with cystic fibrosis.

Supported by Vertex Pharmaceuticals.

Dr. Taylor-Cousar reports receiving fees for serving on advisory boards from Gilead, Novartis, Genentech, Proteostasis, and Vertex Pharmaceuticals, consulting fees from Vertex Pharmaceuticals, and grants paid to her institution from Bayer, Gilead, Celtaxsys, and Vertex Pharmaceuticals; Dr. Munck, receiving fees for serving on an advisory board from Vertex Pharmaceuticals and Novartis and lecture fees from Mayoly Spindler; Dr. McKone, receiving grant support, lecture fees, and travel support from Gilead, fees for serving on an advisory board and travel support from Novartis, grant support, fees for serving on an advisory board, and consulting fees from Vertex Pharmaceuticals, lecture fees and fees for serving on an advisory board from PTC Therapeutics, and fees for serving on an advisory board from Proteostasis; Dr. van der Ent, receiving grant support from Vertex Pharmaceuticals, Gilead, and Galapagos, grant support and fees for serving on an advisory board paid to his institution from ProQR, and lecture fees paid to his institution from Teva Pharmaceuticals; Dr. Moeller, receiving consulting fees from Vertex Pharmaceuticals and Novartis and fees for serving on an advisory board from Gilead; Drs. Simard, Wang, Ingenito, McKee, and Lekstrom-Himes, being employed by and holding equity in Vertex Pharmaceuticals; and Dr. Elborn receiving grant support from Novartis and grant support and fees for serving on an advisory board for ProQR. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families, the trial coordinators, and the investigators for their roles in the trial; Steven Rowe, M.D., M.S.P.H., Jane Davies, M.D., M.B., Ch.B., and Neil Ahluwalia, M.D., for contributions to leadership of the overall clinical trial program; Leah Eardley, M.D., of Vertex Pharmaceuticals, for editorial coordination and assistance; and Jeremy Kennard, Ph.D., Dena McWain, B.A., and Joshua Safran, B.A., of Ashfield Healthcare Communications, for medical writing and editorial assistance with an earlier version of the manuscript, funded by Vertex Pharmaceuticals.

REFERENCES

1. Elborn JS. Cystic fibrosis. Lancet 2016; 388:2519-31.
2. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet 2009;373:1891-904.
3. Cystic Fibrosis Foundation. Clinical and Functional TRanslation of CFTR (CFTR2). Baltimore: Johns Hopkins University (http://cftr2.org/index.php).
4. ECFS Patient Registry: annual data report: 2014 data. Karup, Denmark: European Cystic Fibrosis Society, 2016 (https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports).
5. Cystic Fibrosis Foundation Patient Registry: 2015 annual data report. Bethesda, MD: Cystic Fibrosis Foundation, 2016 (https://www.cff.org/Our-Research/CF-Patient-Registry/2015-Patient-Registry-Annual-Data-Report.pdf).
6. The Canadian Cystic Fibrosis Registry: 2015 annual report. Cystic Fibrosis Canada, 2017. (http://www.cysticfibrosis.ca/uploads/Registry%20Report%202015/2015%20Registry%20Annual%20Report%20EN.pdf).
7. Dalemans W, Barbry P, Champigny G, et al. Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. Nature 1991;354:526-8.
8. Lukacs GL, Chang XB, Bear C, et al.

The delta F508 mutation decreases the stability of cystic fibrosis transmembrane conductance regulator in the plasma membrane: determination of functional half-lives on transfected cells. J Biol Chem 1993;268:21592-8.
9. Van Goor F, Straley KS, Cao D, et al. Rescue of DeltaF508-CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. Am J Physiol Lung Cell Mol Physiol 2006; 290:L1117-L1130.
10. Van Goor F, Hadida S, Grootenhuis PD, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci U S A 2009;106:18825-30.
11. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a *G551D* mutation. Am J Respir Crit Care Med 2013;187:1219-25.
12. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-*G551D* gating mutation. J Cyst Fibros 2014;13:674-80.
13. McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the *Gly551Asp-CFTR* mutation: a phase 3, open-label extension study (PERSIST). Lancet Respir Med 2014;2:902-10.
14. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the *G551D* mutation. N Engl J Med 2011;365:1663-72.
15. Kalydeco (ivacaftor). Boston: Vertex Pharmaceuticals, 2017 (package insert) (http://pi.vrtx.com/files/uspi_ivacaftor.pdf).
16. Van Goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. J Cyst Fibros 2014;13:29-36.
17. Bessonova L, Higgins M, Volkova N, et al. Analysis of real-world outcomes in patients with CF treated with ivacaftor from the 2014 US and UK CF registries. Pediatr Pulmonol 2016;51:Suppl 45:S381. abstract.
18. Van Goor F, Hadida S, Grootenhuis PD, et al. Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. Proc Natl Acad Sci U S A 2011;108:18843-8.
19. Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med 2017;5:107-18.
20. Milla CE, Ratjen F, Marigowda G, et al. Lumacaftor/ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for F508del-CFTR. Am J Respir Crit Care Med 2017;195:912-20.
21. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del *CFTR*. N Engl J Med 2015;373: 220-31.
22. Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med 2017;5:557-67.
23. Sawicki GS, McKone EF, Pasta DJ, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and Cystic Fibrosis Patient Registry data. Am J Respir Crit Care Med 2015;192:836-42.
24. Hubert D, Chiron R, Camara B, et al. Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease. J Cyst Fibros 2017;16:388-91.
25. Jennings MT, Dezube R, Paranjape S, et al. An observational study of outcomes and tolerances in patients with cystic fibrosis initiated on lumacaftor/ivacaftor. Ann Am Thorac Soc 2017 April 13 (Epub ahead of print).
26. Labaste A, Ohlmann C, Mainguy C, et al. Real-life acute lung function changes after lumacaftor/ivacaftor first administration in pediatric patients with cystic fibrosis. J Cyst Fibros 2017 May 18 (Epub ahead of print).
27. Orkambi (lumacaftor/ivacaftor). Boston: Vertex Pharmaceuticals, 2016 (package insert) (http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf).
28. Van Goor F, Grootenhuis PD, Hadida S, et al. Nonclinical profile of the CFTR corrector VX-661. Pediatr Pulmonol 2016; 51:Suppl 45:S274. abstract.
29. Donaldson SH, Pilewski JM, Griese M, et al. Tezacaftor/ivacaftor in subjects with cystic fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. Am J Respir Crit Care Med 2017 September 20 (Epub ahead of print).
30. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75-88.
31. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87.
32. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. Chest 2009;135:1610-8.
33. Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. J Cyst Fibros 2010;9:250-6.
34. MacKenzie T, Gifford AH, Sabadosa KA, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation Patient Registry. Ann Intern Med 2014;161:233-41.
35. Bradley JM, Blume SW, Balp MM, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. Eur Respir J 2013; 41:571-7.
36. de Boer K, Vandemheen KL, Tullis E, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. Thorax 2011;66:680-5.
37. Konstan MW, Wagener JS, Vandevanter DR, et al. Risk factors for rate of decline in FEV_1 in adults with cystic fibrosis. J Cyst Fibros 2012;11:405-11.
38. Stephenson AL, Tom M, Berthiaume Y, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. Eur Respir J 2015;45:670-9.
39. Centers for Disease Control and Prevention. About adult BMI. 2017 (https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html).