Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: a double-blind, randomised, phase 3 trial

Harry G M Heijerman, Edward F McKone*, Damian G Downey, Eva Van Braeckel, Steven M Rowe, Elizabeth Tullis, Marcus A Mall, John J Welter, Bonnie W Ramsey, Charlotte M McKee, Gautham Marigowda, Samuel M Moskowitz, David Waltz, Patrick R Sosnay, Christopher Simard, Neil Ahluwalia, Fengjuan Xuan, Yaohua Zhang, Jennifer L Taylor-Cousar*, Karen S McCoy*, on behalf of the VX17-445-103 Trial Group†*

Summary

Background Cystic fibrosis transmembrane conductance regulator (CFTR) modulators correct the basic defect caused by CFTR mutations. Improvements in health outcomes have been achieved with the combination of a CFTR corrector and potentiator in people with cystic fibrosis homozygous for the *F508del* mutation. The addition of elexacaftor (VX-445), a next-generation CFTR corrector, to tezacaftor plus ivacaftor further improved F508del-CFTR function and clinical outcomes in a phase 2 study in people with cystic fibrosis homozygous for the *F508del* mutation.

Methods This phase 3, multicentre, randomised, double-blind, active-controlled trial of elexacaftor in combination with tezacaftor plus ivacaftor was done at 44 sites in four countries. Eligible participants were those with cystic fibrosis homozygous for the *F508del* mutation, aged 12 years or older with stable disease, and with a percentage predicted forced expiratory volume in 1 s ($ppFEV_1$) of 40–90%, inclusive. After a 4-week tezacaftor plus ivacaftor run-in period, participants were randomly assigned (1:1) to 4 weeks of elexacaftor 200 mg orally once daily plus tezacaftor 100 mg orally once daily plus ivacaftor 150 mg orally every 12 h versus tezacaftor 100 mg orally once daily plus ivacaftor 150 mg orally every 12 h alone. The primary outcome was the absolute change from baseline (measured at the end of the tezacaftor plus ivacaftor run-in) in $ppFEV_1$ at week 4. Key secondary outcomes were absolute change in sweat chloride and Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) score. This study is registered with ClinicalTrials.gov, NCT03525548.

Findings Between Aug 3 and Dec 28, 2018, 113 participants were enrolled. Following the run-in, 107 participants were randomly assigned (55 in the elexacaftor plus tezacaftor plus ivacaftor group and 52 in the tezacaftor plus ivacaftor group) and completed the 4-week treatment period. The elexacaftor plus tezacaftor plus ivacaftor group had improvements in the primary outcome of $ppFEV_1$ (least squares mean [LSM] treatment difference of 10·0 percentage points [95% CI 7·4 to 12·6], p<0·0001) and the key secondary outcomes of sweat chloride concentration (LSM treatment difference –45·1 mmol/L [95% CI –50·1 to –40·1], p<0·0001), and CFQ-R RD score (LSM treatment difference 17·4 points [95% CI 11·8 to 23·0], p<0·0001) compared with the tezacaftor plus ivacaftor group. The triple combination regimen was well tolerated, with no discontinuations. Most adverse events were mild or moderate; serious adverse events occurred in two (4%) participants receiving elexacaftor plus tezacaftor plus ivacaftor and in one (2%) receiving tezacaftor plus ivacaftor.

Interpretation Elexacaftor plus tezacaftor plus ivacaftor provided clinically robust benefit compared with tezacaftor plus ivacaftor alone, with a favourable safety profile, and shows the potential to lead to transformative improvements in the lives of people with cystic fibrosis who are homozygous for the *F508del* mutation.

Funding Vertex Pharmaceuticals.

Published **Online** October 31, 2019 https://doi.org/10.1016/S0140-6736(19)32597-8

See **Online/Comment** https://doi.org/10.1016/S0140-6736(19)32676-5

*Contributed equally

†Members of the VX17-445-103 Trial Group are listed in the appendix

Department of Pulmonology, University Medical Center Utrecht, Utrecht, Netherlands (Prof H G M Heijerman MD); **St Vincent's University Hospital and University College Dublin School of Medicine, Dublin, Ireland** (E F McKone MD); **Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK** (D G Downey MD); **Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium** (E Van Braeckel MD); **Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, USA** (S M Rowe MD); **Division of Respirology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada** (E Tullis MD); **Department of Pulmonology, Immunology and Intensive Care Medicine, Charité–Universitätsmedizin Berlin, Berlin, Germany** (M A Mall MD); **Berlin Institute of Health, Berlin, Germany** (M A Mall); **German Center for Lung Research, Berlin, Germany** (M A Mall); **Division of Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine, New York Medical College, Valhalla, NY, USA** (J J Welter MD); **Department of Pediatrics, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA, USA**

Introduction

Cystic fibrosis is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes the CFTR protein, an anion transporter responsible for conductance of chloride and bicarbonate across epithelial surfaces in the airway, gastrointestinal and reproductive tracts, pancreas, and sweat glands.[1] An absence or reduction in the quantity or function of CFTR, or both, results in abnormal mucus secretions and multiorgan dysfunction, including pancreatic insufficiency and airway infection and obstruction.[1,2] Chronic airway infection leads to progressive lung damage and eventually respiratory failure and premature death, with a median age at death of approximately 31 years.[3–5]

Although more than 2000 variants of the *CFTR* gene are known to exist,[6] the most prevalent disease-causing

(B W Ramsey MD); **Vertex Pharmaceuticals, Boston, MA,USA** (C M McKee MD, G Marigowda MD, S M Moskowitz MD, D Waltz MD, P R Sosnay MD, C Simard MD, N Ahluwalia MD, F Xuan PhD, Y Zhang PhD); **Department of Medicine and Pediatrics, National Jewish Health, Denver, CO, USA** (J L Taylor-Cousar MD); **and Department of Pediatrics, Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA** (K S McCoy MD)

Correspondence to: Prof Harry G M Heijerman, Department of Pulmonology, University Medical Center Utrecht, Heidelberglaan 100 3584CX, Utrecht, Netherlands **h.g.m.heijerman@umcutrecht.nl**

See Online for appendix

Research in context

Evidence before this study

F508del, the most common defective form of the cystic fibrosis transmembrane conductance regulator protein (F508del-CFTR), can be corrected with currently available dual modulator combinations. Treatment of people with cystic fibrosis homozygous for the *F508del* mutation with these dual combinations has resulted in clinical improvements, but these improvements are lower in magnitude than those observed in the small subset of people with cystic fibrosis with genotypes highly responsive to available modulators. In a phase 2 study, addition of a next-generation CFTR corrector, elexacaftor (VX-445), to the existing CFTR modulator dual combination of tezacaftor plus ivacaftor provided further benefit to this group of people with cystic fibrosis. The phase 2, double-blind, active-comparator study of elexacaftor plus tezacaftor plus ivacaftor in a small number of people with cystic fibrosis homozygous for the *F508del* mutation who were already receiving tezacaftor plus ivacaftor showed that the triple drug combination was well tolerated and that the addition of elexacaftor resulted in improvements in lung function, CFTR function, and a patient-reported outcome measure that reports respiratory symptoms. A PubMed search of clinical trials, with no restrictions on publication date or language, with the search terms "elexacaftor" or "VX-445", or both, done on July 30, 2019, revealed only one publication, describing the above-mentioned phase 2 study of elexacaftor plus tezacaftor plus ivacaftor.

Added value of this study

The present study is the first phase 3 trial of elexacaftor plus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for the *F508del* mutation. The results demonstrate, in a larger cohort, profound improvements in lung function, CFTR function, and respiratory-related quality of life with the triple combination regimen compared with tezacaftor plus ivacaftor, along with a favourable safety profile. Evidence of a systemic effect was also seen, with rapid improvements in bodyweight—an important predictor of survival in cystic fibrosis.

Implications of all the available evidence

The introduction of the triple combination of elexacaftor plus tezacaftor plus ivacaftor could extend highly effective CFTR modulator therapy to those homozygous for the *F508del* mutation—a large proportion of people with cystic fibrosis. This advance in therapy is likely to modify the natural course of the disease, leading to meaningful improvements in the lives of people with cystic fibrosis, and profoundly affecting the face of cystic fibrosis care.

CFTR mutation worldwide is *F508del*.[4,5] Up to 90% of all people with cystic fibrosis have at least one copy of this mutation, and almost 50% of people with cystic fibrosis are homozygous for *F508del*.[3–5]

At present, most treatments for people with cystic fibrosis address the downstream complications of CFTR dysfunction, independently of the *CFTR* genetic defect. Small molecules have been developed to address the basic defect through modulation of CFTR protein function. The first CFTR modulator therapy to be developed and approved was ivacaftor, a highly effective CFTR modulator in people with cystic fibrosis who have the *G551D* mutation.

Ivacaftor successfully potentiates this CFTR protein by increasing the open probability of the channel, and led to unprecedented improvements in sweat chloride (an in-vivo marker of CFTR function), lung function, respiratory-related quality of life, bodyweight, and pulmonary exacerbations, which were all sustained over 48 weeks in a placebo-controlled trial.[7]

Ivacaftor alone does not restore F508del-CFTR function;[8] CFTR dysfunction caused by *F508del* is multifactorial, with defective protein processing and trafficking to the cell surface, reduced channel gating, and high turnover once at the cell surface.[2,9,10] However, these defects can be partially overcome with a combination of CFTR modulators. Correctors such as lumacaftor and tezacaftor aid in processing and trafficking of the protein to the cell surface, and the potentiator ivacaftor addresses the gating defect.

Studies of lumacaftor plus ivacaftor and tezacaftor plus ivacaftor showed improvements in lung function (2·6–4·0 percentage points of the percentage predicted forced expiratory volume in 1 s [ppFEV$_1$]) and decreases in the rate of pulmonary exacerbations (a reduction of 35–39%) in people with cystic fibrosis homozygous for the *F508del* mutation.[11,12]

Given the multiple defects in F508del-CFTR affecting processing and trafficking, the magnitude of clinical improvements was consistent with the degree of correction of F508del-CFTR by a single CFTR corrector.[13,14] To further enhance the modulation of F508del-CFTR, it was hypothesised that the addition of a second corrector to a corrector–potentiator combination, acting with a complementary mechanism of action, would be necessary to more fully restore CFTR processing and trafficking.

Elexacaftor (VX-445) is a next-generation CFTR corrector that was shown, in vitro, to substantially increase the amount of mature CFTR protein and CFTR activity when added to the combination of tezacaftor plus ivacaftor.[15] The triple combination of elexacaftor plus tezacaftor plus ivacaftor showed encouraging results in a phase 2 study of a small sample of people with cystic fibrosis homozygous for the *F508del* mutation.[15] The present study was done as part of an ongoing development programme to evaluate the efficacy of elexacaftor plus tezacaftor plus ivacaftor compared with tezacaftor plus ivacaftor alone and to evaluate its safety, in people with cystic fibrosis homozygous for the *F508del* mutation.[16]

Methods

Study design and participants

This phase 3, multicentre, randomised, double-blind, active-controlled trial of elexacaftor in combination with tezacaftor plus ivacaftor was done at 44 sites in four countries (Belgium, the Netherlands, the UK, and the USA). An independent review board or ethics committee for each site approved the trial protocol and informed consent forms. All enrolled participants, or their legal guardians, provided written informed consent (and assent, when appropriate).

Male and female participants aged 12 years and older with a confirmed diagnosis of cystic fibrosis, homozygous for the *F508del* mutation, with $ppFEV_1$ between 40% and 90% inclusive,[17] and stable cystic fibrosis as judged by the investigators were eligible for recruitment. All participants agreed to continue their usual standard-of-care treatment regimens throughout the trial period. The full inclusion and exclusion criteria are provided in the appendix (p 3).

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio by an interactive web response system to receive either elexacaftor plus tezacaftor plus ivacaftor or tezacaftor plus ivacaftor (for additional details see the appendix p 3). Placebo tablets were used to maintain the masking. Randomisation was stratified by $ppFEV_1$ (<70% *vs* ≥70%, as determined during the run-in period) and age (<18 *vs* ≥18 years at the screening visit). At trial completion, participants were given the option to enrol in a 96-week open-label extension trial (VX17-445-105; NCT03525574).

Procedures

Because treatment with lumacaftor plus ivacaftor or tezacaftor plus ivacaftor is standard of care for people with cystic fibrosis homozygous for *F508del*, and to ensure a reliable on-treatment baseline before the triple combination treatment period, participants completed a 4-week tezacaftor plus ivacaftor run-in period following a 4-week screening period, as described by Taylor-Cousar and colleagues.[16]

Participants then received 4 weeks of treatment with either elexacaftor 200 mg once daily in triple combination with tezacaftor 100 mg once daily and ivacaftor 150 mg every 12 h, or the dual combination of tezacaftor 100 mg once daily and ivacaftor 150 mg every 12 h. All drugs were administered orally. Selection of the dose of elexacaftor was based on data from the phase 2 dose-ranging trial.[15] Tezacaftor and ivacaftor were used at the approved dosages in both groups (figure 1).

Outcomes

The primary outcome was the absolute change from baseline in $ppFEV_1$ at week 4. Key secondary outcomes were the absolute change from baseline at week 4 in sweat chloride concentration and in the Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) score. Other secondary outcomes included safety and tolerability (as assessed by investigator-reported adverse events, clinical laboratory values, electrocardiograms, vital signs, and pulse oximetry).

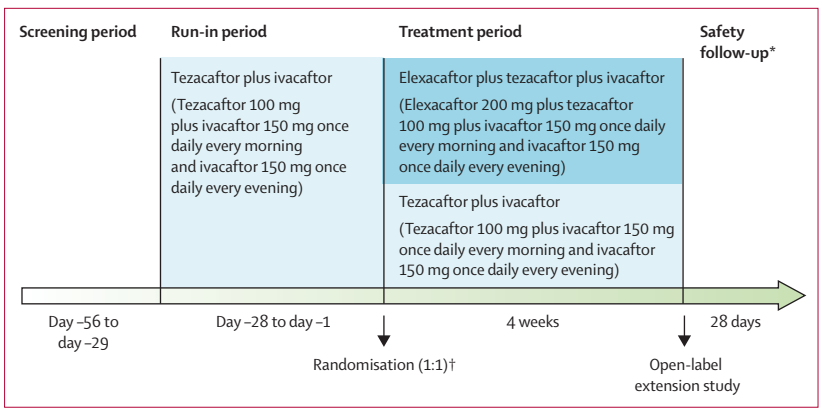

Figure 1: **Study design**

Eligible participants received tezacaftor plus ivacaftor therapy during a 4-week run-in period. After completing the run-in period, participants were randomly assigned (1:1) to receive triple combination therapy (elexacaftor plus tezacaftor plus ivacaftor) or tezacaftor plus ivacaftor for 4 weeks. Randomisation was stratified by predicted FEV_1 (<70% *vs* ≥70%) determined during the run-in period and age (<18 *vs* ≥18 years) determined at the screening visit. FEV_1=forced expiratory volume in 1 s. *Participants who completed the trial regimen were eligible to enrol in a separate 96-week open-label extension study within 28 days after the last dose of trial drug; a safety follow-up visit was required for all participants unless they completed the week 4 visit and enrolled in the open-label extension study. †Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of trial drug in the treatment period (ie, elexacaftor plus tezacaftor plus ivacaftor *vs* tezacaftor plus ivacaftor).

Statistical analysis

Efficacy analyses included all randomly assigned participants who received at least one dose of elexacaftor plus tezacaftor plus ivacaftor or tezacaftor plus ivacaftor in the treatment period. The absolute change from baseline in $ppFEV_1$ at week 4 was analysed by use of a mixed-effects model for repeated measures with change from baseline in $ppFEV_1$ at day 15 and week 4 as the dependent variables. The model included treatment group, visit, and treatment-by-visit interaction as fixed effects, with the continuous baseline $ppFEV_1$ and age at screening (<18 *vs* ≥18 years) as covariates; the model used an unstructured covariance for the within-subject errors.

The trial was designed for superiority. Assuming a within-group SD of 7 percentage points and accounting for a 5% dropout rate at week 4, based on a two-sided, two-sample *t* test at a significance level of 0·05, a sample size of 50 participants per treatment group was expected to achieve more than 90% power to detect a difference of 5 percentage points in the mean absolute change in the $ppFEV_1$ from baseline at week 4 between the two treatment groups. Key secondary outcomes of absolute change in sweat chloride concentration and in CFQ-R RD score were analysed with a similar mixed-effects model for repeated measures.

A hierarchical testing procedure was used to control the overall type I error at an α of 0·05 for the primary outcome and the key secondary outcomes tested. Safety

	Tezacaftor plus ivacaftor group (n=52)	Elexacaftor plus tezacaftor plus ivacaftor group (n=55)
Sex		
Female	28 (54%)	31 (56%)
Male	24 (46%)	24 (44%)
Age at baseline		
Mean age, years	27·9 (10·8)	28·8 (11·5)
Distribution*		
≥12 to <18 years	14 (27%)	16 (29%)
≥18 years	38 (73%)	39 (71%)
Geographical region		
North America	33 (63%)	34 (62%)
Europe	19 (37%)	21 (38%)
$ppFEV_1$		
Mean $ppFEV_1$	60·2 (14·4)	61·6 (15·4)
Distribution		
<40%†	4 (8%)	6 (11%)
≥40% to <70%	34 (65%)	31 (56%)
≥70% to ≤90%	14 (27%)	18 (33%)
>90%	0	0
Mean body-mass index (kg/m^2)	21·88 (4·12)	21·75 (3·19)
Mean sweat chloride concentration, mmol/L	90·0 (12·3)	91·4 (11·0)
Mean CFQ-R respiratory domain score‡	72·6 (17·9)	70·6 (16·2)
Pseudomonas aeruginosa-positive within previous 2 years	31 (60%)	39 (71%)
Previous medication use§		
Dornase alfa		
Yes	48 (92%)	51 (93%)
No	4 (8%)	4 (7%)
Azithromycin		
Yes	25 (48%)	33 (60%)
No	27 (52%)	22 (40%)
Inhaled antibiotic		
Yes	28 (54%)	35 (64%)
No	24 (46%)	20 (36%)
Bronchodilator		
Yes	47 (90%)	54 (98%)
No	5 (10%)	1 (2%)
Inhaled hypertonic saline		
Yes	41 (79%)	38 (69%)
No	11 (21%)	17 (31%)
Inhaled corticosteroids		
Yes	28 (54%)	36 (65%)
No	24 (46%)	19 (35%)
(Table 1 continues in next column)		
(Continued from previous column)		
CFTR modulator therapy		
Yes	34 (65%)	32 (58%)
No	18 (35%)	23 (42%)

Data are n (%) or mean (SD). CFQ-R=Cystic Fibrosis Questionnaire-Revised. CFTR=cystic fibrosis transmembrane conductance regulator. FEV_1=forced expiratory volume in 1 s. $ppFEV_1$=percentage of predicted FEV_1. *Age distribution was calculated on the basis of age at the time of screening. †Although those eligible for enrolment were required to have a $ppFEV_1$ of 40% or higher at screening, some participants had a decrease to a value lower than 40% at baseline. ‡Scores on the CFQ-R range from 0 to 100, with higher scores indicating a higher participant-reported quality of life with regard to respiratory status. §Includes medications administered during the 56 days before the first dose of trial drug in the treatment period.

Table 1: **Demographics and clinical characteristics at baseline**

analyses included all participants who received at least one dose of elexacaftor plus tezacaftor plus ivacaftor or tezacaftor plus ivacaftor in the treatment period.

Safety data were summarised with descriptive statistics. Safety was monitored by an independent data monitoring committee.

This study is registered with ClinicalTrials.gov, NCT03525548.

Role of the funding source

This study was designed by Vertex Pharmaceuticals, in collaboration with the authors. Data were collected by local site investigators and analysed by Vertex Pharmaceuticals, in collaboration with the authors. Vertex Pharmaceuticals was also involved in the writing of the report. All authors had full access to the trial data after the data were unblinded following final database lock and provided critical review and input. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Aug 3 and Dec 28, 2018, 113 participants were enrolled. Following the 4-week tezacaftor plus ivacaftor run-in period, 107 participants were randomly assigned and received at least one dose of the trial drug; 55 in the elexacaftor plus tezacaftor plus ivacaftor group and 52 in the tezacaftor plus ivacaftor group. All 107 participants completed the 4-week treatment period and entered the open-label triple combination regimen extension trial (figure 1; appendix p 5). Demographics and baseline characteristics were similar between the two treatment groups (table 1).

Treatment with elexacaftor plus tezacaftor plus ivacaftor was found to be superior to tezacaftor plus ivacaftor, leading to a rapid improvement in $ppFEV_1$ above the baseline established after 4 weeks of treatment with tezacaftor plus ivacaftor (figure 2; table 2). The least squares mean difference between elexacaftor plus tezacaftor plus ivacaftor and tezacaftor plus ivacaftor in absolute $ppFEV_1$ was 10·0 percentage points (95% CI 7·4 to 12·6; p<0·0001) at week 4.

Consistent with the clinically and statistically significant improvements observed in $ppFEV_1$, elexacaftor plus

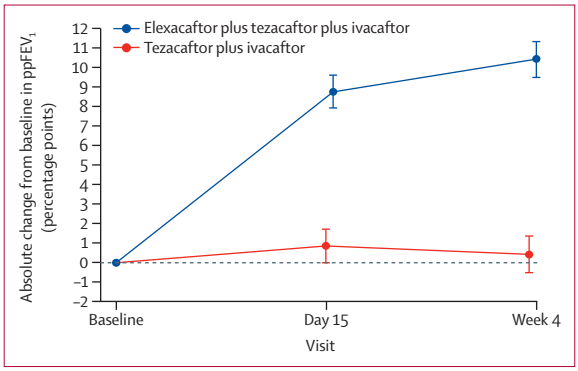

Figure 2: **Absolute change over time in ppFEV$_1$ from baseline**
Data are least squares means based on a mixed-effects model for repeated measures. Error bars indicate standard errors. The dashed line indicates no change from baseline (measured at the end of the tezacaftor plus ivacaftor run-in). ppFEV$_1$=percentage predicted forced expiratory volume in 1 s.

	Tezacaftor plus ivacaftor group (n=52)	Elexacaftor plus tezacaftor plus ivacaftor group (n=55)	Difference* (95% CI)	p value†
Primary outcome				
Absolute change in ppFEV$_1$ from baseline at week 4, percentage points	0·4 (−1·4 to 2·3)	10·4 (8·6 to 12·2)	10·0 (7·4 to 12·6)	<0·0001
Key secondary outcomes				
Absolute change in sweat chloride concentration from baseline at week 4, mmol/L	1·7 (−1·9 to 5·3)	−43·4 (−46·9 to −40·0)	−45·1 (−50·1 to −40·1)	<0·0001
Absolute change in CFQ-R respiratory domain score from baseline at week 4, points	−1·4 (−5·4 to 2·6)	16·0 (12·1 to 19·9)	17·4 (11·8 to 23·0)	<0·0001

Data are least squares means with 95% CIs. CFQ-R=Cystic Fibrosis Questionnaire-Revised. FEV$_1$=forced expiratory volume in 1 s. ppFEV$_1$=percentage of predicted FEV$_1$. *Least squares mean difference between the elexacaftor plus tezacaftor plus ivacaftor group and the tezacaftor plus ivacaftor group on the basis of the mixed-effects model for repeated measures. Baseline was defined as the end of the 4-week tezacaftor plus ivacaftor run-in period. †p values are for the between-group comparisons in all cases.

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

tezacaftor plus ivacaftor resulted in an improvement in sweat chloride concentration, with a least squares mean treatment difference of –45·1 mmol/L at week 4 (95% CI –50·1 to –40·1; p<0·0001) compared with the tezacaftor plus ivacaftor group (figure 3A; table 2); the resulting mean value is below the diagnostic threshold for cystic fibrosis (figure 3B).[18,19] The difference in the change in CFQ-R RD score with elexacaftor plus tezacaftor plus ivacaftor versus with tezacaftor plus ivacaftor was 17·4 points (95% CI 11·8 to 23·0, p<0·0001). In the elexacaftor plus tezacaftor plus ivacaftor group, there was a least squares mean increase in the CFQ-R RD score of 16·0 points (95% CI 12·1 to 19·9; figure 4; table 2), which exceeds the known 4-point improvement corresponding to the minimal clinically important difference in people with cystic fibrosis who have stable disease.[20]

The improvements in ppFEV$_1$ and sweat chloride concentration were consistent across all subgroups evaluated (appendix pp 6–7). The histograms of treatment response for ppFEV$_1$, sweat chloride concentration, and CFQ-R RD score are shown in the appendix (pp 8–10). At week 4, treatment with elexacaftor plus tezacaftor plus ivacaftor resulted in a least squares mean increase in body-mass index (BMI) of 0·60 kg/m² (95% CI 0·41 to 0·79; nominal p<0·0001) and a least squares mean bodyweight increase of 1·6 kg (95% CI 1·0 to 2·1; nominal p<0·0001) compared with tezacaftor plus ivacaftor. Because these analyses were not predefined, they were not corrected for multiplicity and p values are considered nominal.

Elexacaftor plus tezacaftor plus ivacaftor was generally safe and well tolerated in this 4-week trial. Adverse events occurred in 32 (58%) participants in the elexacaftor plus tezacaftor plus ivacaftor group and in 33 (63%) in the tezacaftor plus ivacaftor group (table 3). The vast majority of adverse events resolved during the study.

No participants in the elexacaftor plus tezacaftor plus ivacaftor group and one (2%) in the tezacaftor plus ivacaftor group had an adverse event reported as severe.

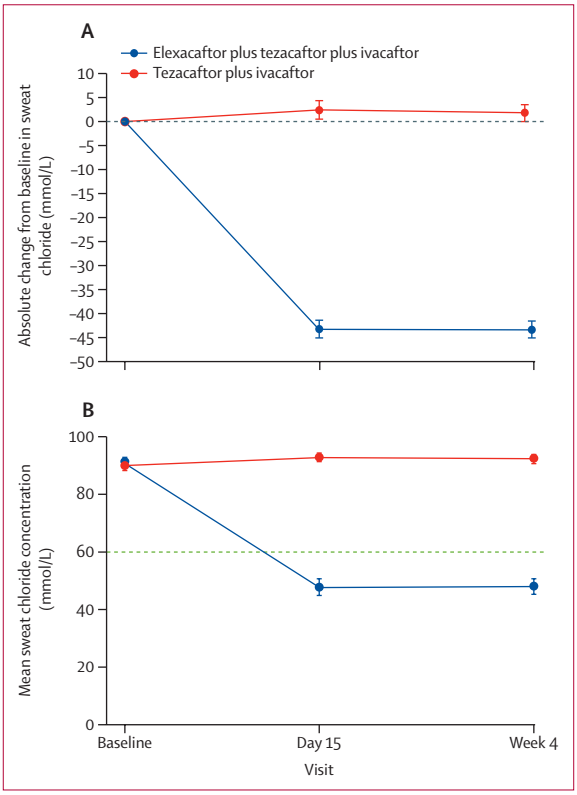

Figure 3: **Absolute change over time in sweat chloride concentration from baseline**
(A) Absolute change in sweat chloride concentrataion from baseline, measured at the end of the tezacaftor plus ivacaftor run-in period. (B) Mean sweat chloride concentration for each treatment group by visit. Data are least squares means based on a mixed-effects model for repeated measures for panel A and sample means for panel B. Error bars indicate standard errors. The dashed grey line in panel A indicates no change from baseline; the dashed green line in panel B indicates the 60 mmol/L diagnostic threshold for sweat chloride concentration.[18]

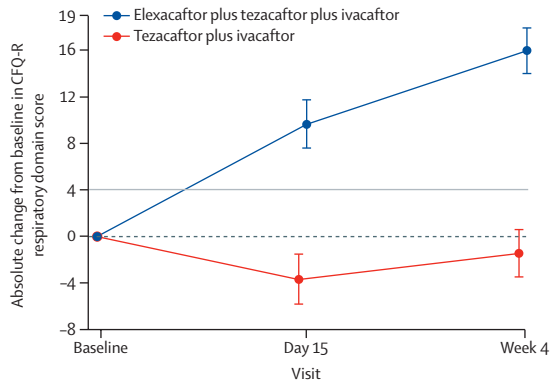

Figure 4: **Absolute change over time in CFQ-R respiratory domain score from baseline**

Scores range from 0 to 100, with higher scores indicating a higher participant-reported quality of life with regard to respiratory status. Data are least squares mean based on a mixed-effects model for repeated measures. Error bars indicate standard errors. The dashed line indicates no change from baseline. The solid light grey line indicates a change in 4 points, which is the minimal clinically important difference for people with cystic fibrosis with stable disease.[20] CFQ-R=Cystic Fibrosis Questionnaire-Revised.

All other adverse events were mild or moderate. There were no adverse events that led to discontinuation of the trial regimen in either treatment group. Serious adverse events occurred in two (4%) participants in the elexacaftor plus tezacaftor plus ivacaftor group (rash in one participant and pulmonary exacerbation in another) and in one (2%) participant in the tezacaftor plus ivacaftor group (pulmonary exacerbation).

The most common adverse events, occurring in more than 10% of participants in either treatment group, were cough and pulmonary exacerbation. Cough occurred more frequently in the elexacaftor plus tezacaftor plus ivacaftor group than in the tezacaftor plus ivacaftor group (15% *vs* 8%), whereas pulmonary exacerbation occurred more often in the tezacaftor plus ivacaftor group (2% *vs* 12%). Adverse events occurring in at least four participants in either treatment group are shown in table 3.

Investigators reported elevated aminotransferase concentrations as adverse events in two (4%) participants in the elexacaftor plus tezacaftor plus ivacaftor group and in one (2%) participant in the tezacaftor plus ivacaftor group; each investigator assessed the event as mild in severity and not serious. Review of laboratory results showed an incidence of alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal in four (7%) participants, more than five times the upper limit of normal in two (4%), and more than eight times the upper limit of normal in no participants in the elexacaftor plus tezacaftor plus ivacaftor group, and in no participants at any of these thresholds in the tezacaftor plus ivacaftor group.

No participants had elevations of alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal concurrent with an elevation in total bilirubin more than two times the upper limit of normal. No aminotransferase elevations required study drug interruption or discontinuation.

	Tezacaftor plus ivacaftor group (n=52)	Elexacaftor plus tezacaftor plus ivacaftor group (n=55)
Any adverse event	33 (63%)	32 (58%)
Adverse event related to trial drug*	9 (17%)	12 (22%)
Adverse event, according to maximum severity		
Mild	21 (40%)	23 (42%)
Moderate	11 (21%)	9 (16%)
Severe	1 (2%)	0
Life threatening	0	0
Grade 3 or 4 adverse event	1 (2%)	0
Serious adverse event	1 (2%)	2 (4%)
Serious adverse event related to trial drug*	0	1 (2%)
Adverse event leading to discontinuation of trial drug	0	0
Adverse event leading to death	0	0
Most common adverse events†		
Cough	4 (8%)	8 (15%)
Nasopharyngitis	2 (4%)	4 (7%)
Oropharyngeal pain	0	4 (7%)
Upper respiratory tract infection	2 (4%)	4 (7%)
Headache	4 (8%)	3 (5%)
Haemoptysis	5 (10%)	2 (4%)
Pulmonary exacerbation‡	6 (12%)	1 (2%)

Data are n (%). Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1. When summarising number and proportion of participants, a participant with multiple events within a category was counted only once in that category. *Relatedness to trial drug was determined by the investigators. When summarising the number of participants with adverse events or serious adverse events related to the trial drug, adverse events with relationship of related, possibly related, and missing were counted. †The most common adverse events were those that occurred in at least four participants in either trial group. ‡Per MedDRA 21.1, this adverse event is coded as infective pulmonary exacerbation of cystic fibrosis.

Table 3: **Adverse events**

Rash was seen in two (4%) participants in the elexacaftor plus tezacaftor plus ivacaftor group and in two (4%) participants in the tezacaftor plus ivacaftor group. All four participants with rash were female, and all events were mild in severity; none required interruption or discontinuation of the trial drugs. Both rash events in participants receiving elexacaftor plus tezacaftor plus ivacaftor resolved during the trial. One participant in each treatment group who had rash was receiving a concomitant hormonal oral contraceptive; the participant receiving elexacaftor plus tezacaftor plus ivacaftor discontinued the hormonal oral contraceptive. The safety profile was consistent among subgroups (age, baseline ppFEV$_1$, sex, and geographical region). No clinically relevant differences were observed between the two treatment groups in vital signs, oximetry, physical examinations, laboratory abnormalities, or electrocardiogram findings.

Discussion

In this phase 3 trial in people with cystic fibrosis homozygous for the *F508del* mutation, in which all participants had a 4-week pre-treatment period with tezacaftor plus ivacaftor, treatment with the triple combination regimen of elexacaftor plus tezacaftor plus ivacaftor resulted in substantial improvements in lung function, sweat chloride concentration, respiratory-related quality of life, and nutritional parameters compared with tezacaftor plus ivacaftor alone. Similar results were observed across all subgroups. Elexacaftor plus tezacaftor plus ivacaftor was well tolerated, with a safety profile comparable to that in the group receiving tezacaftor plus ivacaftor alone. The most commonly reported adverse events were consistent with typical manifestations of cystic fibrosis.

To date, clinical results following treatment with ivacaftor in people with cystic fibrosis with the *G551D* mutation are considered to be the benchmark for treatment with highly effective CFTR modulators. Following 24 weeks of ivacaftor therapy, the increase in $ppFEV_1$ of 10·6 percentage points and a substantial reduction in pulmonary exacerbations compared with placebo[7] were sustained in a 96-week trial.[21] Ivacaftor therapy has also been shown to be associated with a decreased need for lung transplant and improved survival with long-term use.[22,23]

Comparatively, people with cystic fibrosis homozygous for *F508del* treated with tezacaftor plus ivacaftor had an increase in $ppFEV_1$ of 4 percentage points compared with placebo.[12] The 10·0-percentage-point improvement in lung function with elexacaftor plus tezacaftor plus ivacaftor compared with tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for *F508del* observed in the current trial is similar to that seen with ivacaftor in people with cystic fibrosis and the *G551D* mutation.[7]

Data from the 96-week open-label study of the triple combination regimen in people with cystic fibrosis who are homozygous or heterozygous for *F508del* (ClinicalTrials.gov, NCT03525574) will be obtained to confirm the sustainability of these outcomes over a longer period of time.

To understand how the effects of the triple combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation would have compared if a placebo control, rather than an active control, had been used, the improvements in clinical outcomes and CFTR function previously reported in this population for tezacaftor plus ivacaftor over placebo should be considered. In the current trial, participants started the triple combination regimen after a run-in with tezacaftor plus ivacaftor. The treatment effect of tezacaftor plus ivacaftor is reflected in the baseline sweat chloride concentration of 90 mmol/L, which is comparable to that observed at the end of the tezacaftor plus ivacaftor versus placebo trial,[12] and approximately 10 mmol/L below that in untreated people with cystic fibrosis homozygous for *F508del*.

The addition of elexacaftor to tezacaftor plus ivacaftor in this trial resulted in a mean sweat chloride concentration of 48·0 mmol/L at week 4, which is below the diagnostic threshold for cystic fibrosis (60 mmol/L).[18] Likewise, the improvements in lung function (10 percentage points in $ppFEV_1$) observed with elexacaftor plus tezacaftor plus ivacaftor compared with tezacaftor plus ivacaftor in the present trial might be taken into context with the demonstrated impact of tezacaftor plus ivacaftor in this population (a 4-percentage-point improvement in $ppFEV_1$ compared with placebo).[12] It is useful to frame these results observed in trial participants taking elexacaftor plus tezacaftor plus ivacaftor, and the magnitude of CFTR modulation they represent, in the context of the overall degree of CFTR modulation and the clinical benefits observed in people with cystic fibrosis and a *G551D* mutation treated with ivacaftor.[7]

Benefits of the triple combination regimen were also observed for other important outcomes, including surrogates for nutritional health. Although the treatment duration in this trial was only 4 weeks, an increase in BMI and bodyweight was observed in the elexacaftor plus tezacaftor plus ivacaftor group compared with participants who received tezacaftor plus ivacaftor alone. Improvements in bodyweight and BMI were not observed in a 24-week study of tezacaftor plus ivacaftor in the same population.[12] Weight and BMI in people with cystic fibrosis are closely correlated with improvements in lung function and are independent predictors of survival.[24,25] The improvements in weight and BMI over 4 weeks observed herein are therefore promising.

Pulmonary exacerbations are important life events for people with cystic fibrosis and are associated with a greater rate of lung function decline and decreased survival.[24,26] Although not defined as an efficacy outcome in this 4-week trial, there was a reduction in reported adverse events of infective pulmonary exacerbation of cystic fibrosis in the elexacaftor plus tezacaftor plus ivacaftor group compared with the tezacaftor plus ivacaftor group. These results and those observed in the longer companion trial in people with cystic fibrosis heterozygous for the *F508del* mutation, in which treatment with elexacaftor plus tezacaftor plus ivacaftor resulted in a 63% reduction in pulmonary exacerbations compared with placebo,[27] provide encouraging evidence of the effect of this triple combination regimen on pulmonary exacerbations compared with the current standard of care.

Most phase 3 trials assessing the efficacy of CFTR modulators have used treatment periods of 24 weeks or longer, and a potential limitation of this trial is the 4-week duration.[7,11,12] However, a 4-week duration was selected for this trial on the basis of observations that short-term changes in lung function have consistently been shown within 4 weeks of treatment with CFTR modulators in previous randomised controlled trials, and that these short-term improvements in lung function have been sustained through 24 weeks of treatment.[7,11,12] The 4-week duration of this trial is also based on the premise that the safety profile observed in the concurrent 24-week trial of elexacaftor plus

tezacaftor plus ivacaftor in people with cystic fibrosis heterozygous for *F508del*[27] would be applicable to people with cystic fibrosis homozygous for *F508del*. The second assumption is supported by previous data with CFTR modulators showing comparable safety data across numerous cystic fibrosis genotypes.[7,8,28] Long-term outcomes of elexacaftor plus tezacaftor plus ivacaftor will be evaluated in ongoing investigations, including the open-label extension of this trial and post-approval observational studies.

In conclusion, the results of this phase 3 trial demonstrate the efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor in participants homozygous for *F508del* over a 4-week study period. In the concurrent phase 3 trial in people with cystic fibrosis in whom a single *F508del* mutation was responsible for the treatment response, marked improvements in clinical outcomes substantiate the ability of the triple combination regimen to restore F508del-CFTR function.[27]

Based on the known impact of the benchmark therapy ivacaftor in a small subset of people with cystic fibrosis, the introduction of elexacaftor plus tezacaftor plus ivacaftor is expected to lead to meaningful improvements in the lives of people with cystic fibrosis homozygous for *F508del*. This degree of CFTR modulation in such a large proportion of people with cystic fibrosis could profoundly affect the face of cystic fibrosis care.

Contributors

The VX17-445-103 study was designed by the study sponsor, Vertex Pharmaceuticals, in collaboration with EFM, SMR, ET, MAM, BWR, and JLT-C. HGMH, DGD, EVB, JJW, JLT-C, and KSM enrolled participants and collected the data, which were analysed by the sponsor. All authors participated in the analysis and interpretation of study data, drafting and critically revising the manuscript for important intellectual content, and gave final approval of the manuscript for publication.

Declaration of interests

HGMH reports speaker fees from Chiesi, Horizon Pharma, PTC Therapeutics, TEVA, and Vertex; and fees for advisory board participation from Vertex and PTC Therapeutics. EFM reports grants from Gilead and Vertex, for which his institution (St Vincent's University Hospital, Dublin, Ireland) received payment; consulting fees from Vertex and Proteostasis; and non-financial support from Novartis. DGD reports grants from Chiesi, Gilead, Proteostasis and Vertex, for which his institution (Queen's University Belfast, Belfast, UK) received payment; speaker fees from Gilead and Vertex; and honoraria from Gilead and Proteostasis. EVB reports research grants from Vertex, Galapagos, and Zambon, for which her institution (Ghent University Hospital, Ghent, Belgium) received payment; and fees for advisory board participation for Vertex. SMR reports research grants from AstraZeneca, Bayer, Celtaxys, Eloxx, Forest Research Institute, Galapagos/AbbVie, N30/Nivalis, Novartis, PTC Therapeutics, Synedgen/Synspira, and Vertex, for which his institution (University of Alabama at Birmingham, Birmingham, AL, USA) received payment; consulting fees from Bayer, Celtaxys, Novartis, Renovion, Synedgen/Synspira, and Vertex; and fees for advisory board participation for Vertex. ET reports grants from AbbVie, Proteostasis, and Vertex, for which her institution (St Michael's Hospital, London, UK) received payment; and personal fees from Proteostasis and Vertex. MAM reports research grants from Vertex, for which his institution (Charité-Universitätsmedizin Berlin, Germany) received payment; consulting fees from Bayer, Galapagos, and Sterna Biologicals; fees for consulting and advisory board participation from Arrowhead, Boehringer Ingelheim, Enterprise Therapeutics, Polyphor, ProQR Therapeutics, Sathera, Spyryx Bioscience, and Vertex; and speaker fees from Bayer, Boehringer Ingelheim, Celtaxys, and Vertex. JJW reports grants from Concert, Proteostasis, and Vertex, for which his institution (New York Medical College, New York, NY, USA) received payment. CMM, GM, SMM, DW, PRS, CS, NA, FX, and YZ are employees of Vertex and may own stock or stock options in that company. JLT-C reports research grants from Celtaxys, Bayer, Gilead, National Institutes of Health, Proteostasis, the Cystic Fibrosis Foundation, and Vertex, for which her institution (National Jewish Health, Denver, CO, USA) received payment; consulting fees from Celtaxys, Proteostasis, Santhera, and Vertex; fees for advisory board participation from Gilead, Protalix, and Vertex; speaker fees from Celtaxys, Proteostasis, and Vertex; and service on the Cystic Fibrosis Foundation Therapeutics Development Network Clinical Research Executive Committee and is Chair-Elect of the American Thoracic Society Clinical Problems Assembly Programming Committee. KSM reports research grants from Alcresta, Corbus, Novoteris, Proteostasis, Savara, Translate Bio, and Vertex, for which her institution (Nationwide Children's Hospital, Columbus, OH, USA) received payment. BWR declares no competing interests.

Data sharing

Vertex Pharmaceuticals is committed to advancing medical science and improving patient health. This commitment includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex Pharmaceuticals and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.

Acknowledgments

We thank the participants and their families for participating and the study investigators and coordinators for their contributions to the study. We thank the Cystic Fibrosis Foundation Therapeutics Development Network and the European Cystic Fibrosis Clinical Trials Network for their support of the study sites. The study was supported by Vertex Pharmaceuticals. The National Institutes of Health provided grant support to the University of Alabama at Birmingham (P30DK072482, R35HL135816, and U54TR001368) and Seattle Children's Hospital (P30-DK-089507, 5UL1 TR 0002319, and 1U01TR 002487). Editorial coordination and support were provided by Sarah Garber and Swati Thorat. SG is a former employee of Vertex Pharmaceuticals, and ST is an employee of Vertex Pharmaceuticals and may own stock or stock options in the company. Editorial assistance was provided by Katherine Mills-Lujan of ArticulateScience under the guidance of the authors and was supported by Vertex Pharmaceuticals.

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