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Safety and efficacy of vanzacaftor–tezacaftor–deutivacaftor in adults with cystic fibrosis: randomised, double-blind, controlled, phase 2 trials



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Summary

Background Elexacaftor–tezacaftor–ivacaftor has been shown to be safe and efficacious in people with cystic fibrosis and at least one *F508del* allele. Our aim was to identify a novel cystic fibrosis transmembrane conductance regulator (CFTR) modulator combination capable of further increasing CFTR-mediated chloride transport, with the potential for once-daily dosing.

Methods We conducted two phase 2 clinical trials to assess the safety and efficacy of a once-daily combination of vanzacaftor–tezacaftor–deutivacaftor in participants with cystic fibrosis who were aged 18 years or older. A phase 2 randomised, double-blind, active-controlled study (VX18-561-101; April 17, 2019, to Aug 20, 2020) was carried out to compare deutivacaftor monotherapy with ivacaftor monotherapy in participants with *CFTR* gating mutations, following a 4-week ivacaftor monotherapy run-in period. Participants were randomly assigned to receive either ivacaftor 150 mg every 12 h, deutivacaftor 25 mg once daily, deutivacaftor 50 mg once daily, deutivacaftor 150 mg once daily, or deutivacaftor 250 mg once daily in a 1:1:2:2:2 ratio. The primary endpoint was absolute change in ppFEV₁ from baseline at week 12. A phase 2 randomised, double-blind, controlled, proof-of-concept study of vanzacaftor–tezacaftor–deutivacaftor (VX18-121-101; April 30, 2019, to Dec 10, 2019) was conducted in participants with cystic fibrosis and heterozygous for *F508del* and a minimal function mutation (*F/MF* genotypes) or homozygous for *F508del* (*F/F* genotype). Participants with *F/MF* genotypes were randomly assigned 1:2:2:1 to receive either 5 mg, 10 mg, or 20 mg of vanzacaftor in combination with tezacaftor–deutivacaftor or a triple placebo for 4 weeks, and participants with the *F/F* genotype were randomly assigned 2:1 to receive either vanzacaftor (20 mg)–tezacaftor–deutivacaftor or tezacaftor–ivacaftor active control for 4 weeks, following a 4-week tezacaftor–ivacaftor run-in period. Primary endpoints for part 1 and part 2 were safety and tolerability and absolute change in ppFEV₁ from baseline to day 29. Secondary efficacy endpoints were absolute change from baseline at day 29 in sweat chloride concentrations and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score. These clinical trials are registered with ClinicalTrials.gov, NCT03911713 and NCT03912233, and are complete.

Findings In study VX18-561-101, participants treated with deutivacaftor 150 mg once daily (n=23) or deutivacaftor 250 mg once daily (n=24) had mean absolute changes in ppFEV₁ of 3·1 percentage points (95% CI –0·8 to 7·0) and 2·7 percentage points (–1·0 to 6·5) from baseline at week 12, respectively, versus –0·8 percentage points (–6·2 to 4·7) with ivacaftor 150 mg every 12 h (n=11); the deutivacaftor safety profile was consistent with the established safety profile of ivacaftor 150 mg every 12 h. In study VX18-121-101, participants with *F/MF* genotypes treated with vanzacaftor (5 mg)–tezacaftor–deutivacaftor (n=9), vanzacaftor (10 mg)–tezacaftor–deutivacaftor (n=19), vanzacaftor (20 mg)–tezacaftor–deutivacaftor (n=20), and placebo (n=10) had mean changes relative to baseline at day 29 in ppFEV₁ of 4·6 percentage points (–1·3 to 10·6), 14·2 percentage points (10·0 to 18·4), 9·8 percentage points (5·7 to 13·8), and 1·9 percentage points (–4·1 to 8·0), respectively, in sweat chloride concentration of –42·8 mmol/L (–51·7 to –34·0), –45·8 mmol/L (95% CI –51·9 to –39·7), –49·5 mmol/L (–55·9 to –43·1), and 2·3 mmol/L (–7·0 to 11·6), respectively, and in CFQ-R respiratory domain score of 17·6 points (3·5 to 31·6), 21·2 points (11·9 to 30·6), 29·8 points (21·0 to 38·7), and 3·3 points (–10·1 to 16·6), respectively. Participants with the *F/F* genotype treated with vanzacaftor (20 mg)–tezacaftor–deutivacaftor (n=18) and tezacaftor–ivacaftor (n=10) had mean changes relative to baseline (taking tezacaftor–ivacaftor) at day 29 in ppFEV₁ of 15·9 percentage points (11·3 to 20·6) and –0·1 percentage points (–6·4 to 6·1), respectively, in sweat chloride concentration of –45·5 mmol/L (–49·7 to –41·3) and –2·6 mmol/L (–8·2 to 3·1), respectively, and in CFQ-R respiratory domain score of 19·4 points (95% CI 10·5 to 28·3) and –5·0 points (–16·9 to 7·0), respectively. The most common adverse events overall were cough, increased sputum, and headache. One participant in the vanzacaftor–tezacaftor–deutivacaftor group had a serious adverse event of infective pulmonary exacerbation and another participant had a serious rash event that led to treatment discontinuation. For most participants, adverse events were mild or moderate in severity.

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Interpretation Once-daily dosing with vanzacaftor–tezacaftor–deutivacaftor was safe and well tolerated and improved lung function, respiratory symptoms, and CFTR function. These results support the continued investigation of vanzacaftor–tezacaftor–deutivacaftor in phase 3 clinical trials compared with elexacaftor–tezacaftor–ivacaftor.

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Introduction

Cystic fibrosis is a life-limiting autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes an ion channel involved in the transport of chloride and bicarbonate.^{1,2} Disease-causing *CFTR* mutations result in a reduction in quantity or function, or both, of the CFTR protein.³ Cystic fibrosis affects more than 80 000 people worldwide,⁴ with approximately 90% having at least one *F508del-CFTR* allele, the most common *CFTR* mutation.³ The natural history of cystic fibrosis shows that the amount of CFTR-mediated chloride transport (as measured by sweat chloride) correlates with the severity and course of disease,⁵ with carriers of one cystic fibrosis-causing mutation typically having no symptoms and no clinical evidence of CFTR dysfunction.

CFTR modulators are small molecules that treat the underlying cause of cystic fibrosis and include potentiators (eg, ivacaftor), which increase channel opening or gating activity of the CFTR protein, and correctors (eg, tezacaftor and elexacaftor), which improve the processing and trafficking of the CFTR protein to the cell surface.³ A triple-combination regimen of elexacaftor–tezacaftor–ivacaftor was shown to be efficacious and safe

in phase 3 pivotal trials^{4,6,7} and was first approved for use in 2019 for people with cystic fibrosis aged 12 years and older with at least one *F508del* allele.^{8,9} In these studies, elexacaftor–tezacaftor–ivacaftor treatment led to robust improvements in lung function (assessed by percent predicted FEV₁ [ppFEV₁]), respiratory symptoms (assessed by Cystic Fibrosis Questionnaire-Revised [CFQ-R] respiratory domain score), and CFTR function (assessed by sweat chloride concentration), exceeding the clinical benefits reported with previous CFTR modulators in this patient population.^{4,6} Long-term study data up to 144 weeks after completion of pivotal studies have shown that these clinical improvements are durable, with no mean decline in lung function and no new safety concerns identified,¹⁰ and real-world studies have shown a decreased risk of pulmonary exacerbations, lung transplantation, and death in patients treated with elexacaftor–tezacaftor–ivacaftor.¹¹ These findings have established elexacaftor–tezacaftor–ivacaftor as a transformative treatment option for patients with cystic fibrosis who have at least one *F508del* allele.

Although elexacaftor–tezacaftor–ivacaftor improves CFTR function, leading to broad clinical benefit,^{7–9} only a small percentage of people with cystic fibrosis taking elexacaftor–tezacaftor–ivacaftor achieve sweat chloride

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See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE using the terms “elexacaftor”, “clinical trial”, and “CFTR modulator” for clinical trials of CFTR modulators from database inception through Sept 26, 2022, with no language restrictions. Current CFTR modulator therapies, such as elexacaftor–tezacaftor–ivacaftor, have transformed cystic fibrosis care. However, further increasing cystic fibrosis transmembrane conductor regulator (CFTR)-mediated chloride transport to correct the basic defect causing cystic fibrosis, as well as simplifying dosing regimens, offers the potential for additional clinical benefit to people with cystic fibrosis.

Added value of this study

We report results from two phase 2 clinical trials designed to assess a novel once-daily triple combination of vanzacaftor–tezacaftor–deutivacaftor in people with cystic fibrosis who have at least one *F508del* allele. Treatment with vanzacaftor–tezacaftor–deutivacaftor was safe and well tolerated, with most

participants having adverse events that were mild or moderate in severity and generally consistent with manifestations of cystic fibrosis, and led to improvements in lung function, respiratory symptoms, and CFTR function. Greater reductions in sweat chloride concentrations were observed in participants with *F/MF* and *F/F* genotypes given vanzacaftor–tezacaftor–deutivacaftor in the current study than in participants with *F/MF* and *F/F* genotypes in the elexacaftor–tezacaftor–ivacaftor phase 2 study.

Implications of all the available evidence

The current studies show that vanzacaftor in triple combination with tezacaftor and deutivacaftor is safe and efficacious in adults with cystic fibrosis who have *F/MF* or *F/F* genotypes. The favourable benefit–risk profile, along with the potential to be superior to elexacaftor–tezacaftor–ivacaftor in restoring CFTR function, support further investigation of vanzacaftor–tezacaftor–deutivacaftor in phase 3 trials against elexacaftor–tezacaftor–ivacaftor, the standard-of-care treatment for cystic fibrosis.

concentrations similar to those seen in people with a single copy of a cystic fibrosis-causing mutation (cystic fibrosis carriers) who typically have no symptoms. This suggests that it might be possible to develop even more efficacious CFTR modulators that could further enhance CFTR function in people with cystic fibrosis. The goal of the vanzacaftor–tezacaftor–deutivacaftor programme is to develop a CFTR modulator combination capable of providing a greater improvement in CFTR-mediated chloride transport (a measure of CFTR function, as measured by a further reduction in sweat chloride) compared with elxacaftor–tezacaftor–ivacaftor, with the additional convenience of a once-daily dosing regimen to improve adherence. Vanzacaftor is a novel CFTR corrector, whereas deutivacaftor (VX-561) is a novel CFTR potentiator that has been shown to have a reduced rate of clearance, increased exposure, greater plasma concentrations at 24 h, and a longer half-life compared with ivacaftor, thereby supporting once-daily dosing.^{12,13}

Here, we present data from two phase 2 clinical studies designed to assess the safety and efficacy of the triple combination of vanzacaftor–tezacaftor–deutivacaftor, as well as determine optimal dosing for phase 3 development of this once-daily CFTR modulator regimen.

Methods

Study design and participants

The effects of vanzacaftor on the processing, trafficking, and function of F508del-CFTR protein were evaluated in in-vitro studies by means of human bronchial epithelial (HBE) cells derived from people with cystic fibrosis. Immunoblotting methods by means of HBE cells from an *F/MF* donor and assessments of chloride transport, as measured in HBE cells from donors with *F/MF* or *F/F* genotypes by means of an Ussing chamber, are detailed in the appendix (p 5).

VX18-561-101 was a phase 2, randomised, double-blind, parallel-group, active-controlled trial conducted at 40 sites in North America, Europe, and Australia designed to assess the efficacy and safety of deutivacaftor monotherapy in people with cystic fibrosis aged 18 years or older with a *CFTR* gating mutation and who were previously stable on ivacaftor monotherapy to facilitate deutivacaftor dose selection for future clinical trials.

VX18-121-101 was a phase 2, randomised, double-blind, controlled, proof-of-concept study done at 26 sites in the USA, UK, Germany, Netherlands, and Portugal to evaluate the safety and efficacy of vanzacaftor–tezacaftor–deutivacaftor in adults with cystic fibrosis aged 18 years or older with ppFEV₁ between 40 and 90 percentage points. This was a multipart study, with parts 1 and 2 done in parallel.

The trials were designed by Vertex Pharmaceuticals in collaboration with the academic authors. Informed consent was obtained from all participants in accordance with local requirements. For all studies, the protocol and amendments, informed consent, and

other necessary documents were reviewed and approved by an independent ethics committee or institutional review board for each study site before initiation. All clinical studies were monitored by an independent data monitoring committee with a prespecified plan to assess participants for potential decompensation in clinical measures as a consequence of inadequate CFTR modulation in the lower dosing groups in study VX18-561-101 (see appendix for protocols).

Randomisation and masking

Third-party vendors generated random code lists, and participants were randomly assigned to groups by means of an interactive web-response system. In both trials, randomisation was stratified by ppFEV₁ at screening (<70 vs ≥70). For VX18-561-101, patients were randomly assigned to ivacaftor 150 mg every 12 h, or 25 mg, 50 mg, 150 mg, or 250 mg of deutivacaftor once daily in a 1:1:2:2:2 ratio for 12 weeks. For VX18-121-101, in part 1, participants with *F/MF* genotypes were randomly assigned 1:2:2:1 to one of three doses of vanzacaftor in triple combination with tezacaftor–deutivacaftor or triple placebo for 4 weeks. In part 2, after completing a 4-week tezacaftor–ivacaftor run-in period, participants with the *F/F* genotype were randomly assigned 2:1 to either vanzacaftor in triple combination with tezacaftor–deutivacaftor or to tezacaftor–ivacaftor alone (masked active control) for 4 weeks. For the phase 2 clinical trials reported here, all participants, site personnel, and the sponsor's study team were masked to treatment codes, and all tablets given were matched in size and appearance to maintain the masking.

Procedures

For VX18-561-101, after a 4-week ivacaftor monotherapy (150 mg every 12 h) run-in period, patients received either 25 mg, 50 mg, 150 mg, or 250 mg of deutivacaftor once daily or ivacaftor 150 mg every 12 h for 12 weeks (figure 1A). Additional details on study design and complete participant inclusion and exclusion criteria (including eligible *CFTR* gating mutations) are provided in the appendix (pp 8–10).

For VX18-121-101, in part 1, participants with *F/MF* genotypes received either 5 mg, 10 mg, or 20 mg vanzacaftor in triple combination with tezacaftor–deutivacaftor or triple placebo for 4 weeks followed by an 18 day wash-out period during which participants in the vanzacaftor groups received tezacaftor–deutivacaftor and participants in the triple placebo group received dual placebo. Qualifying minimal function mutations and other eligibility criteria are provided in the appendix (pp 15–16; figure 1C).

In part 2, after completing a 4-week tezacaftor–ivacaftor run-in period, participants with the *F/F* genotype received either 20 mg vanzacaftor in triple combination with tezacaftor–deutivacaftor or tezacaftor–ivacaftor alone (masked active control) for a 4-week treatment period,

followed by a 4-week wash-out period during which all participants received tezacaftor–ivacaftor. Tezacaftor–ivacaftor was chosen for the run-in and as the masked active control because it was the approved standard of care for patients with the *F/F* genotype at the time of study conduct (figure 1D).

Outcomes

For VX18-561-101, the primary endpoint was absolute change in ppFEV₁ from baseline at week 12. Secondary endpoints included safety and tolerability and absolute change in sweat chloride concentration from baseline at week 12. Analyses of primary and secondary efficacy endpoints included all randomly assigned participants who received at least one dose of study drug or control.

Vanzacaftor was firstly assessed in a phase 1–2 study in triple combination with tezacaftor–ivacaftor (VX17-121-001) and then with tezacaftor–deutivacaftor (VX18-121-101). Details on the design and results of the phase 1–2 study of vanzacaftor–tezacaftor–ivacaftor in people with cystic fibrosis who were aged 18 years or older who have *F/MF* genotypes can be found in figure 1B and in the appendix (pp 5–6, 11).

For VX18-121-101, primary endpoints were safety and tolerability and absolute change in ppFEV₁ from baseline to day 29 in people with cystic fibrosis who have *F/MF* genotypes (part 1) or *F/F* genotype (part 2). Adverse events were coded using Medical Dictionary for Regulatory Activities version 22.1. Secondary endpoints were absolute change in sweat chloride concentrations from baseline to day 29 and absolute change in CFQ-R respiratory domain score from baseline at day 29.

Statistical analyses

For VX18-561-101, on the basis of the initial study design and assuming a within-group SD of 7 percentage points with a 10% dropout rate at week 12, a sample size of 22 participants in the deutivacaftor 50 mg once daily, 150 mg once daily, and 250 mg once daily treatment groups provided a 95% CI of ± 3.4 percentage points around the observed mean absolute change in ppFEV₁ from baseline at week 12, on the basis of two-sided, one-sample *t* statistics; a sample size of 11 participants in the

deutivacaftor 25 mg once daily and ivacaftor 150 mg every 12 h treatment groups provided a 95% CI of ± 5.4 percentage points around the observed mean. The primary efficacy was analysed by means of a mixed-effects model for repeated measures. The model included the absolute change from baseline in ppFEV₁ at day 15 and

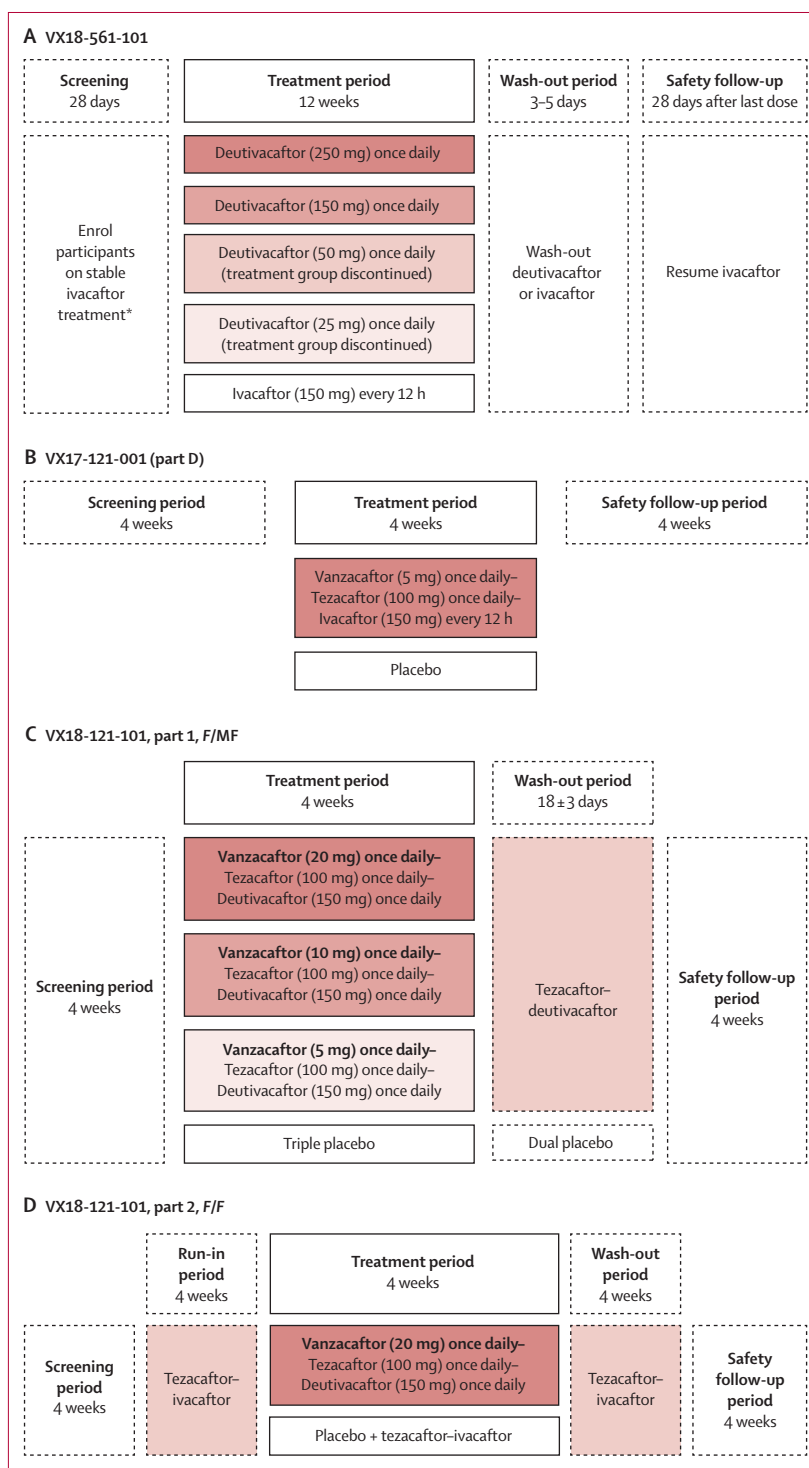


Figure 1: Study designs (A) VX18-561-101, (B) VX17-121-001 (part D), (C) VX18-121-101 (part 1), (D) VX18-121-101 (part 2)

VX18-561-101 was a phase 2 study of deutivacaftor monotherapy (12-week treatment period) in people with cystic fibrosis aged 18 years and older (A). VX17-121-001 (Part D) was a phase 1–2 study of vanzacaftor–tezacaftor–ivacaftor (4-week treatment period) in people with cystic fibrosis aged 18 years and older (B) see appendix pp 5–6, 11. VX18-121-101 was a two-part (part 1 and part 2), phase 2 study of vanzacaftor–tezacaftor–deutivacaftor (4-week treatment period in each part) in people with cystic fibrosis aged 18 years and older with *F/MF* genotypes (C) or the *F/F* genotype (D). *F*=*F508del*-*CFTR*. *MF*=minimal function.

*The deutivacaftor 25 mg once daily and deutivacaftor 50 mg once daily treatment groups were discontinued. The remaining enrolled patients were randomly assigned 2:2:1 to the deutivacaftor 250 mg once a day, deutivacaftor 150 mg once a day, and ivacaftor 150 mg every 12 h treatment groups.

week 4, 8, and 12 with the deutivacaftor 150 mg once daily, deutivacaftor 250 mg once daily, or ivacaftor 150 mg every 12 h treatment groups as the dependent variable; treatment group, visit, and treatment by visit as fixed effects; and baseline ppFEV₁ as a covariate. Efficacy data from the discontinued treatment groups (deutivacaftor 25 mg once daily and deutivacaftor 50 mg once daily) were not included in the model. The primary results obtained from the model were the within-group treatment effect estimate together with two-sided 95% CI at week 12 for each treatment group.

For VX18-121-101, safety analyses included all randomly assigned participants who received at least one dose of study drug or control, and safety data were summarised by means of descriptive statistics. The trial was designed for superiority compared with baseline within a treatment group. A sample size of 18 participants per treatment group provided at least 90% power to detect a mean within-treatment change of 7 percentage points in ppFEV₁, compared with baseline assuming an SD of 8 percentage points. Analyses of primary and secondary efficacy endpoints included all randomly assigned participants who received at least one dose of study drug or control. The primary efficacy was analysed by means of a mixed-effects model for repeated measures, with change from baseline in ppFEV₁ at day 15 and day 29 as the dependent variable for each part separately. The model included treatment group, visit, and treatment-by-visit interaction as fixed effects and participant as a random effect, with the continuous baseline ppFEV₁ as a covariate. The model was estimated by means of restricted maximum likelihood. Denominator degrees of freedom for the F test for fixed effects was estimated by means of the Kenward-Roger approximation. An unstructured covariance structure was used to model the within-subject errors. If the model estimation did not converge, a compound symmetry covariance structure was used instead. Missing ppFEV₁ data were assumed to be missing at random; consequently, no imputation of missing data was done. We did not adjust for multiplicity, so all p values should be considered nominal. These clinical trials are registered with ClinicalTrials.gov, NCT03768089 and NCT03912233.

Role of the funding source

The funder of the study had a role in study design, data analysis, and data interpretation.

Results

It is well established that the magnitude of increase in CFTR function following treatment of HBE cells with CFTR modulators is largely predictive of clinical outcomes in people with cystic fibrosis.^{14–16} In-vitro studies of F508del-CFTR protein in HBE cells derived from donors with *F/F* and *F/MF* genotypes showed that treatment with the triple combination of vanzacaftor–tezacaftor–deutivacaftor resulted in higher concentrations of mature

CFTR protein and higher levels of chloride transport than with tezacaftor–ivacaftor (appendix pp 10, 25–27). These results provided the molecular rationale for investigating vanzacaftor–tezacaftor–deutivacaftor in people with cystic fibrosis and *F/F* or *F/MF* genotypes.

The VX18-561-101 phase 2 study was done between April 17, 2019, and Aug 20, 2020. A total of 77 participants who were previously clinically stable on commercial ivacaftor were randomly assigned to ivacaftor (n=12), deutivacaftor 25 mg (n=6), deutivacaftor 50 mg (n=11), deutivacaftor 150 mg (n=24), and deutivacaftor 250 mg (n=24) groups (appendix pp 10–11). Demographics and baseline characteristics were similar between treatment groups (appendix p 18). Deutivacaftor 150 mg once daily and 250 mg once daily administered as monotherapy for up to 12 weeks was safe and well tolerated; the deutivacaftor safety profile was consistent with the established safety profile of ivacaftor 150 mg every 12 h (appendix p 19). The mean absolute change in ppFEV₁ from baseline at week 12 was 3.1 percentage points (95% CI –0.8 to 7.0) for deutivacaftor 150 mg once daily and 2.7 percentage points (–1.0 to 6.5) for deutivacaftor 250 mg once daily, compared with –0.8 percentage points (–6.2 to 4.7) for ivacaftor 150 mg every 12 h (appendix p 21). The mean change in sweat chloride concentration from baseline at week 12 was 3.3 mmol/L (95% CI –4.6 to 11.2) for deutivacaftor 150 mg and –6.5 mmol/L (–14.1 to 1.2) for deutivacaftor 250 mg, compared with 0.9 mmol/L (–9.5 to 11.3) for ivacaftor 150 mg (appendix p 21). In a decision endorsed by the independent data monitoring committee, Vertex Pharmaceuticals discontinued the deutivacaftor 25 mg and deutivacaftor 50 mg groups in the study after five participants in the deutivacaftor 25 mg or deutivacaftor 50 mg groups had decreases in ppFEV₁, consistent with insufficient CFTR modulation by the lower doses of deutivacaftor. Additional details are provided in the appendix (p 11). Absolute change from baseline in ppFEV₁ and in sweat chloride concentrations at selected visits for the combined low-dose groups are reported in appendix (p 22).

The VX18-121-101 phase 2 study was done between April 30, 2019, and Dec 10, 2019, before elexacaftor–tezacaftor–ivacaftor was approved commercially. Tezacaftor–ivacaftor was the standard-of-care CFTR modulator for patients with the *F/F* genotype, and there was no approved CFTR modulator for patients with the *F/MF* genotype. 58 participants with *F/MF* genotypes were randomly assigned and dosed in part 1 and 28 participants with the *F/F* genotype were randomly assigned and dosed in part 2 (figure 2).

Demographics and baseline characteristics were similar between treatment groups in each part of the study (table 1). In part 1, the mean baseline ppFEV₁ was lower in the placebo group (51.8 percentage points [SD 13.1]) compared with the vanzacaftor–tezacaftor–deutivacaftor groups (vanzacaftor [5 mg]–tezacaftor–deutivacaftor

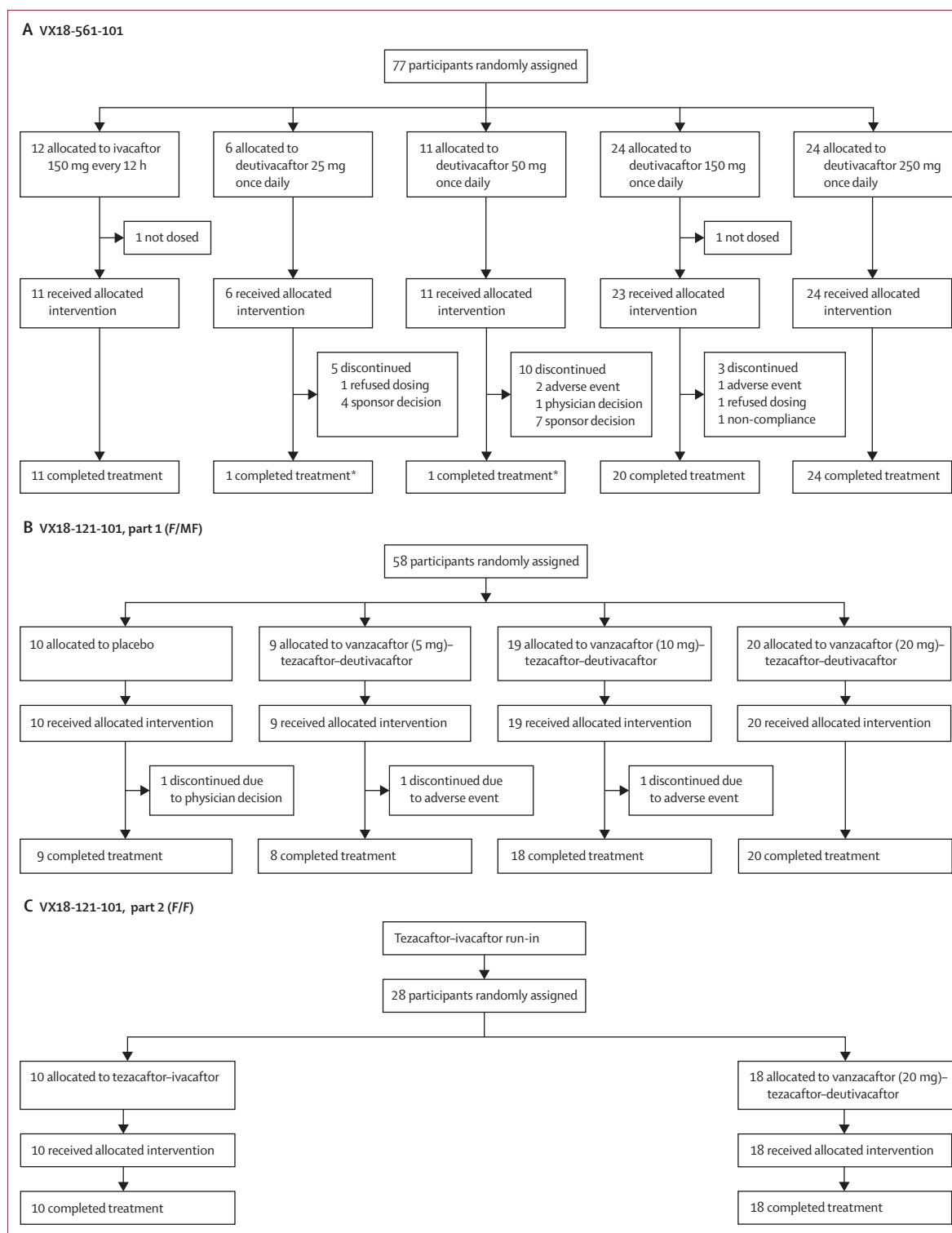


Figure 2: Participant disposition for the phase 2 studies VX18-561-101 and VX18-121-101

*The deuterivacaftor 25 mg and 50 mg groups were discontinued.

	Part 1 (F/MF), full-analysis set				Part 2 (F/F), full-analysis set	
	Placebo (n=10)	Vanzacaftor (5 mg)–tezacaftor–deutivacaftor (n=9)	Vanzacaftor (10 mg)–tezacaftor–deutivacaftor (n=19)	Vanzacaftor (20 mg)–tezacaftor–deutivacaftor (n=20)	Tezacaftor–ivacaftor (n=10)	Vanzacaftor (20 mg)–tezacaftor–deutivacaftor (n=18)
Sex						
Male	8 (80%)	5 (56%)	16 (84%)	11 (55%)	8 (80%)	11 (61%)
Female	2 (20%)	4 (44%)	3 (16%)	9 (45%)	2 (20%)	7 (39%)
Age at baseline, years	30.6 (5.9)	33.0 (11.4)	30.8 (9.1)	36.4 (11.7)	33.0 (8.3)	30.8 (8.7)
Ethnicity						
Hispanic or Latinx	0	0	0	2 (10%)	1 (10%)	0
Not Hispanic or Latinx	10 (100%)	8 (89%)	19 (100%)	17 (85%)	8 (80%)	18 (100%)
Not collected per local regulations	0	1 (11%)	0	1 (5%)	1 (10%)	0
Race*						
White	10 (100%)	8 (89%)	18 (95%)	17 (85%)	9 (90%)	18 (100%)
Black	1 (10%)	0	1 (5%)	0	0	0
Other	0	0	0	2 (10%)	0	0
Not collected per local regulations	0	1 (11%)	0	1 (5%)	1 (10%)	0
Weight, kg	62.9 (7.5)	65.0 (13.1)	67.2 (14.6)	62.5 (11.2)	67.9 (12.0)	67.1 (13.6)
Height, cm	168.5 (10.9)	171.2 (10.4)	171.2 (6.9)	166.1 (8.4)	172.6 (8.2)	171.9 (11.3)
BMI, kg/m ²	22.16 (1.71)	21.98 (2.42)	22.83 (4.09)	22.49 (2.56)	22.84 (4.35)	22.57 (3.14)
ppFEV ₁ (percentage points) at baseline category						
<40	1 (10%)	1 (11%)	1 (5%)	0	1 (10%)	2 (11%)
≥40 to <70	9 (90%)	6 (67%)	14 (74%)	17 (85%)	6 (60%)	11 (61%)
≥70 to ≤90	0	2 (22%)	4 (21%)	3 (15%)	3 (30%)	5 (28%)
ppFEV ₁ (percentage points) at baseline	51.8 (13.1)	62.3 (13.2)	58.4 (13.2)	60.1 (13.0)	57.4 (15.1)	60.9 (15.4)
Sweat chloride (mmol/L) at baseline	101.6 (8.6)	98.8 (4.3)	98.5 (9.3)	98.5 (10.0)	92.2 (10.9)	90.5 (11.7)
CFQ-R RD score (points) at baseline	56.7 (14.8)	67.3 (18.1)	64.0 (19.9)	58.1 (18.9)	69.4 (12.4)	71.3 (17.1)

Data are n (%) or mean (SD). F/MF=heterozygous for F508del and a minimal function mutation. F/F=homozygous for F508del. CFQ-R RD=Cystic Fibrosis Questionnaire-Revised respiratory domain. Full analysis set=all randomly assigned participants who carry the intended cystic fibrosis transmembrane conductance regulator allele mutation(s) and received at least one dose of study drug in the treatment period. ppFEV₁=percent predicted FEV₁. *A participant who is reported to have multiple races is reported under each of those races.

Table 1: Baseline characteristics for phase 2 study VX18-121-101

62.3 percentage points [13.2]; vanzacaftor (10 mg)–tezacaftor–deutivacaftor 58.4 percentage points [13.2]; vanzacaftor (20 mg)–tezacaftor–deutivacaftor 60.1 percentage points [13.0]).

Overall, three participants had adverse events that led to discontinuation (table 2). Most participants had adverse events that were mild or moderate in severity and generally consistent with manifestations of cystic fibrosis. The most common adverse events were cough, increased sputum, and headache (table 2). Two participants in the vanzacaftor–tezacaftor–deutivacaftor group had serious adverse events: infective pulmonary exacerbation in one participant and a rash event in another participant that led to treatment discontinuation. Elevated concentrations of alanine or aspartate aminotransferases more than 3 times and up to 5 times the upper limit of normal occurred in three participants (6%) in the vanzacaftor–tezacaftor–deutivacaftor group (appendix p 23). There were no clinically relevant findings from other laboratory, electrocardiogram, or vital sign assessments.

Treatment with vanzacaftor (5 mg)–tezacaftor–deutivacaftor, vanzacaftor (10 mg)–tezacaftor–deutivacaftor, and vanzacaftor (20 mg)–tezacaftor–deutivacaftor in

participants with F/MF genotypes led to mean absolute changes from baseline in ppFEV₁ of 4.6 percentage points (95% CI –1.3 to 10.6), 14.2 percentage points (10.0 to 18.4), and 9.8 percentage points (5.7 to 13.8), respectively, to day 29 compared with an absolute mean change of 1.9 percentage points (–4.1 to 8.0) for participants receiving placebo (table 3, figure 3A, appendix p 29). Increases in ppFEV₁ from baseline (following the 4-week tezacaftor–ivacaftor run-in period) through day 29 were also seen in participants with F/F genotypes given vanzacaftor (20 mg)–tezacaftor–deutivacaftor (15.9 percentage points [95% CI 11.3 to 20.6]) compared with participants receiving tezacaftor–ivacaftor alone (–0.1 percentage points [–6.4 to 6.1]; table 3, figure 3B, appendix pp 29). Improvements in both sweat chloride concentration and CFQ-R respiratory domain score were also observed in participants with F/MF and F/F genotypes. Mean changes in sweat chloride concentration from baseline to day 29 in participants with F/MF genotypes given vanzacaftor (5 mg)–tezacaftor–deutivacaftor, vanzacaftor (10 mg)–tezacaftor–deutivacaftor, and vanzacaftor (20 mg)–tezacaftor–deutivacaftor were –42.8 mmol/L (95% CI –51.7 to –34.0), –45.8 mmol/L

	Part 1 (F/MF), safety analysis set				Part 2 (F/F), safety analysis set	
	Placebo (n=10)	Vanzacaftor (5 mg)- tezacaftor- deutivacaftor (n=9)	Vanzacaftor (10 mg)- tezacaftor- deutivacaftor (n=19)	Vanzacaftor (20 mg)- tezacaftor- deutivacaftor (n=20)	Tezacaftor- ivacaftor (n=10)	Vanzacaftor (20 mg)- tezacaftor- deutivacaftor (n=18)
Overview of adverse events						
Total adverse events	49	44	82	97	60	50
Participants with any adverse events	9 (90%)	8 (89%)	16 (84%)	20 (100%)	8 (80%)	16 (89%)
Participants with adverse events by strongest relationship						
Not related	3 (30%)	0	2 (11%)	4 (20%)	3 (30%)	4 (22%)
Unlikely related	4 (40%)	1 (11%)	2 (11%)	4 (20%)	2 (20%)	1 (6%)
Possibly related	2 (20%)	7 (78%)	11 (58%)	9 (45%)	3 (30%)	8 (44%)
Related	0	0	1 (5%)	3 (15%)	0	3 (17%)
Participants with adverse events by maximum severity						
Mild	3 (30%)	3 (33%)	8 (42%)	13 (65%)	3 (30%)	10 (56%)
Moderate	5 (50%)	4 (44%)	7 (37%)	7 (35%)	5 (50%)	5 (28%)
Severe	1 (10%)	1 (11%)	1 (5%)	0	0	1 (6%)
Life threatening	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Participants with adverse events leading to study drug discontinuation	0	1 (11%)	2 (11%)	0	0	0
Participants with adverse events leading to study drug interruption	0	0	2 (11%)	0	0	2 (11%)
Participants with serious adverse events	2 (20%)	1 (11%)	1 (5%)	0	0	0
Participants with treatment-related serious adverse events	0	1 (11%)	0	0	0	0
Participants with adverse events leading to death	0	0	0	0	0	0
Adverse events occurring in ≥10% of participants in the vanzacaftor-tezacaftor-deutivacaftor groups in total (part 1) and in the vanzacaftor-tezacaftor-deutivacaftor group (part 2), safety-analysis set						
Cough	5 (50%)	4 (44%)	5 (26%)	9 (45%)	7 (70%)	5 (28%)
Sputum increased	3 (30%)	6 (67%)	3 (16%)	4 (20%)	3 (30%)	5 (28%)
Headache	1 (10%)	2 (22%)	4 (21%)	6 (30%)	1 (10%)	2 (11%)
Diarrhoea	0	0	4 (21%)	5 (25%)	1 (10%)	2 (11%)
Fatigue	0	2 (22%)	5 (26%)	2 (10%)	2 (20%)	0
Infective pulmonary exacerbation of cystic fibrosis	5 (50%)	3 (33%)	1 (5%)	3 (15%)	2 (20%)	0
Oropharyngeal pain	0	2 (22%)	3 (16%)	2 (10%)	0	3 (17%)
Dyspnoea	1 (10%)	1 (11%)	2 (11%)	3 (15%)	2 (20%)	0
Nasopharyngitis	1 (10%)	2 (22%)	2 (11%)	2 (10%)	2 (20%)	2 (11%)
Blood creatine phosphokinase increased	0	1 (11%)	3 (16%)	1 (5%)	0	2 (11%)
Nasal congestion	0	1 (11%)	1 (5%)	3 (15%)	2 (20%)	1 (6%)
Productive cough	3 (30%)	0	2 (11%)	3 (15%)	0	0
Rash	1 (10%)	1 (11%)	0	1 (5%)	0	3 (17%)
Hypoglycaemia	0	0	0	1 (5%)	0	2 (11%)
Data are n (%). Safety-analysis set=all participants who received at least one dose of study drug. Adverse events were coded using Medical Dictionary for Regulatory Activities version 22.1. A participant with multiple events within a category is counted only once in that category.						
Table 2: Summary of adverse events, including overview of treatment-emergent adverse events and most common treatment-emergent adverse events for study VX18121-101						

(−51.9 to −39.7), and −49.5 mmol/L (−55.9 to −43.1), respectively, compared with 2.3 mmol/L (−7.0 to 11.6) for participants receiving placebo; participants with the F/F genotype given vanzacaftor (20 mg)-tezacaftor-deutivacaftor had a mean change in sweat chloride of −45.5 mmol/L (−49.7 to −41.3) compared with −2.6 mmol/L (−8.2 to 3.1) for participants receiving tezacaftor-ivacaftor (table 3, figures 3C–D and appendix p 29). Mean changes in CFQ-R respiratory domain score

from baseline at day 29 in participants with F/MF genotypes given vanzacaftor (5 mg)-tezacaftor-deutivacaftor, vanzacaftor (10 mg)-tezacaftor-deutivacaftor, and vanzacaftor (20 mg)-tezacaftor-deutivacaftor were 17.6 points (95% CI 3.5 to 31.6), 21.2 points (11.9 to 30.6), and 29.8 points (21.0 to 38.7), respectively, compared with 3.3 points (−10.1 to 16.6) for participants receiving placebo; participants with the F/F genotype given vanzacaftor (20 mg)-tezacaftor-deutivacaftor had a mean

	Part 1 (F/MF), full-analysis set				Part 2 (F/F), full-analysis set	
	Placebo (n=10)	Vanzacaftor (5 mg)–tezacaftor–deutivacaftor (n=9)	Vanzacaftor (10 mg)–tezacaftor–deutivacaftor (n=19)	Vanzacaftor (20 mg)–tezacaftor–deutivacaftor (n=20)	Tezacaftor–ivacaftor (n=10)	Vanzacaftor (20 mg)–tezacaftor–deutivacaftor (n=18)
Mixed-effects model for repeated measures analysis of absolute change from baseline* in ppFEV₁ to day 29, percentage points						
Least squares mean (SE)	1.9 (3.0)	4.6 (3.0)	14.2 (2.1)	9.8 (2.0)	-0.1 (3.0)	15.9 (2.3)
95% CI	-4.1 to 8.0	-1.3 to 10.6	10.0 to 18.4	5.7 to 13.8	-6.4 to 6.1	11.3 to 20.6
p value within treatment†	0.52	0.13	<0.0001	<0.0001	0.96	<0.0001
Least squares mean treatment difference	..	2.7	12.3	7.8	..	16.1
95% CI	..	-5.9 to 11.3	4.9 to 19.6	0.4 to 15.2	..	8.2 to 23.9
p value vs placebo or tezacaftor–ivacaftor	..	0.53	0.0016	0.038	..	0.0003
Mixed-effects model for repeated measures analysis of absolute change from baseline* in sweat chloride to day 29, mmol/L						
Least squares mean (SE)	2.3 (4.6)	-42.8 (4.4)	-45.8 (3.0)	-49.5 (3.2)	-2.6 (2.8)	-45.5 (2.0)
95% CI	-7.0 to 11.6	-51.7 to -34.0	-51.9 to -39.7	-55.9 to -43.1	-8.2 to 3.1	-49.7 to -41.3
p value within treatment†	0.62	<0.0001	<0.0001	<0.0001	0.36	<0.0001
Least squares mean treatment difference	..	-45.1	-48.1	-51.8	..	-42.9
95% CI	..	-58.1 to -32.2	-59.2 to -37.0	-63.2 to -40.3	..	-50.0 to -35.8
p value vs placebo or tezacaftor–ivacaftor	..	<0.0001	<0.0001	<0.0001	..	<0.0001
Mixed-effects model for repeated measures analysis of absolute change from baseline* in Cystic Fibrosis Questionnaire—revised respiratory domain score to day 29						
Least squares mean (SE)	3.3 (6.7)	17.6 (7.0)	21.2 (4.7)	29.8 (4.4)	-5.0 (5.8)	19.4 (4.3)
95% CI	-10.1 to 16.6	3.5 to 31.6	11.9 to 30.6	21.0 to 38.7	-16.9 to 7.0	10.5 to 28.3
p value within treatment†	0.63	0.015	<0.0001	<0.0001	0.40	0.0001
Least squares mean treatment difference	..	14.3	18.0	26.6	..	24.4
95% CI	..	-5.2 to 33.8	1.7 to 34.3	10.5 to 42.7	..	9.5 to 39.3
p value vs placebo or tezacaftor–ivacaftor	..	0.15	0.031	0.0017	..	0.0025

F/MF=heterozygous for *F508del* and a minimal function mutation. F/F=homozygous for *F508del*. Full-analysis set=all randomly assigned participants who carry the intended *CFTR* allele mutation[s] and received at least one dose of study drug in the treatment period. ppFEV₁=percent predicted FEV₁. *Baseline is defined as the most recent non-missing measurement before the first dose of vanzacaftor–tezacaftor–ivacaftor in the treatment period. Baseline in part 2 reflects values at the end of the tezacaftor–ivacaftor run-in. †No adjustment for multiplicity was done; p values for the efficacy analyses should be considered nominal.

Table 3: Summary of efficacy results for phase 2 study VX18-121-101

change of 19.4 points (10.5 to 28.3) compared with -5.0 points (-16.9 to 7.0) for participants receiving tezacaftor–ivacaftor (table 3, figure 3E–F).

Discussion

We assessed the safety and efficacy of the novel triple combination regimen vanzacaftor–tezacaftor–deutivacaftor in two phase 2 trials. Preclinical studies showed improved processing and trafficking of *F508del*-CFTR protein as well as increased chloride transport with the addition of vanzacaftor on top of tezacaftor–deutivacaftor. Clinically, vanzacaftor–tezacaftor–deutivacaftor was safe and well tolerated and led to improvements in lung function, respiratory symptoms, and CFTR function in participants with cystic fibrosis who had at least one *F508del* allele.

Sweat chloride is the most proximal measurement of CFTR function, and natural history data from registry studies show that lower concentrations of sweat chloride are associated with reduced mortality and improved clinical outcomes, including a reduced rate of lung function decline, lower rates of lung transplantations, and better nutritional and growth parameters.^{5,17} Moreover, people with only a single copy of a cystic

fibrosis-causing mutation typically have no cystic fibrosis symptoms. Thus, lifelong improvement of sweat chloride concentrations to amounts closer to those seen in asymptomatic carriers is anticipated to further improve short-term and long-term outcomes.

In preclinical studies, the triple combination of vanzacaftor–tezacaftor–deutivacaftor significantly increased the amount of *F508del*-CFTR found at the cell surface and increased chloride transport in HBE cells derived from cystic fibrosis donors, indicating that this triple combination of CFTR modulators improves both CFTR processing–trafficking and function. The magnitude of increase in chloride transport observed in vitro with tezacaftor–deutivacaftor was similar to that previously observed for tezacaftor–ivacaftor, whereas the triple combination of vanzacaftor–tezacaftor–deutivacaftor provided greater increases in both protein processing (as reflected in band C) and CFTR-mediated chloride transport as that seen in preclinical studies of elxacaftor–tezacaftor–ivacaftor.¹⁵ The efficacy of CFTR modulators in the in-vitro HBE system has previously been predictive of clinical results for sweat chloride concentration and clinical outcomes in people with cystic fibrosis. Consistent with this finding, greater reductions

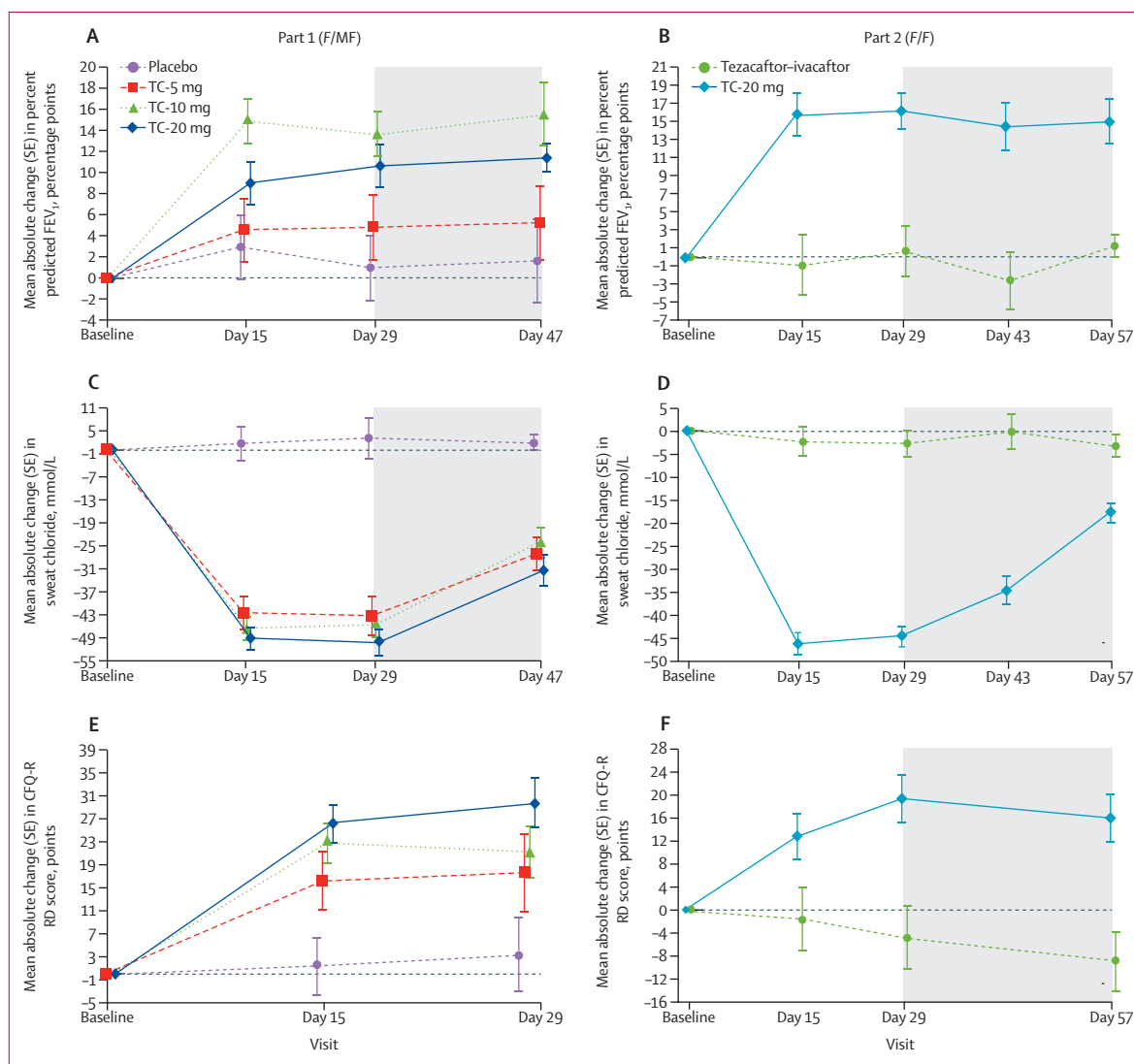


Figure 3: Absolute changes from baseline by visit for study VX18-121-101

(A–B) Percent predicted FEV₁, (C–D) Sweat chloride, (E–F) CFQ-R RD score. Shaded areas represent washout periods. CFQ-R RD=Cystic Fibrosis Questionnaire-Revised respiratory domain. TC=triple combination. TC-5 mg=vanzacaftor 5 mg-tezacaftor 100 mg-deutivacaftor 150 mg once a day. TC-10 mg=vanzacaftor 10 mg-tezacaftor 100 mg-deutivacaftor 150 mg once a day. TC-20 mg=vanzacaftor 20 mg-tezacaftor 100 mg-deutivacaftor 150 mg once a day.

in sweat chloride concentrations were observed in participants with *F/MF* genotypes given vanzacaftor (10 mg)-tezacaftor-deutivacaftor (–45.8 mmol/L compared with baseline) or vanzacaftor (20 mg)-tezacaftor-deutivacaftor (–49.5 mmol/L compared with baseline) and in participants with the *F/F* genotype given vanzacaftor (20 mg)-tezacaftor-deutivacaftor (–45.5 mmol/L compared with baseline [when taking tezacaftor-ivacaftor]) than in participants with *F/MF* and *F/F* genotypes who received elexacaftor-tezacaftor-ivacaftor (–39.1 mmol/L compared with baseline and –39.6 mmol/L compared with baseline [when taking tezacaftor-ivacaftor], respectively) in a phase 2 study.¹⁵

Vanzacaftor-tezacaftor-deutivacaftor treatment also led to clinically meaningful improvements in both ppFEV₁

and CFQ-R respiratory domain score during the 4-week treatment period. The results, expressed as a change from untreated baseline (participants with *F/MF* genotypes) or as a change from tezacaftor-ivacaftor baseline (participants with the *F/F* genotype), were similar to, or better than, improvements seen in patients treated with elexacaftor-tezacaftor-ivacaftor in a phase 2 trial.¹⁵ Specifically, participants with *F/MF* genotypes given vanzacaftor (10 mg)-tezacaftor-deutivacaftor or vanzacaftor (20 mg)-tezacaftor-deutivacaftor had increases in ppFEV₁ (14.2 percentage points and 9.8 percentage points, respectively, compared with baseline) and CFQ-R respiratory domain score (21.2 points and 29.8 points, respectively, compared with baseline) that were consistent with, or larger than, what was previously reported

in participants given elexacaftor–tezacaftor–ivacaftor (13·8 percentage points and 25·7 points, respectively, compared with baseline). Similarly, participants with the *F/F* genotype given vanzacaftor (20 mg)–tezacaftor–deutivacaftor had improvements in both ppFEV₁ (15·9 percentage points compared with baseline [when taking tezacaftor–ivacaftor]) and CFQ-R respiratory domain score (19·4 points compared with baseline [when taking tezacaftor–ivacaftor]) that were consistent with, or larger than, what was previously reported in participants who received elexacaftor–tezacaftor–ivacaftor (11·0 percentage points and 20·7 points, respectively, compared with baseline [when taking tezacaftor–ivacaftor]). On the basis of ppFEV₁ and CFQ-R results, together with the changes in sweat chloride concentrations, vanzacaftor–tezacaftor–deutivacaftor has the potential to be more efficacious than elexacaftor–tezacaftor–ivacaftor.

It should also be noted that vanzacaftor–tezacaftor–ivacaftor is suitable for once-daily dosing, which might reduce barriers to successful treatment and increase adherence, especially among patients taking multiple medications. Once-daily dosing has been made possible by substituting ivacaftor for deutivacaftor, which in phase 1 clinical studies in healthy participants had a reduced clearance rate, increased exposure with greater plasma concentrations at 24 h, and a longer half-life compared with ivacaftor.¹⁸ At clinically relevant doses of deutivacaftor, safety data were consistent with the established safety profile of ivacaftor. Efficacy results showed that treatment with either deutivacaftor 250 mg once daily or deutivacaftor 150 mg once daily resulted in similar absolute values of ppFEV₁ compared with ivacaftor 150 mg treatment every 12 h, whereas treatment with deutivacaftor 250 mg once daily resulted in numerically greater improvements in sweat chloride concentration compared with deutivacaftor 150 mg once daily and ivacaftor 150 mg every 12 h. The totality of the evidence suggests that deutivacaftor 250 mg once daily might provide greater restoration of CFTR function and additional clinical benefit compared with deutivacaftor 150 mg once daily and ivacaftor 150 mg every 12 h.

A limitation of the current studies, similar to other phase 2 proof-of-concept studies, is the small sample sizes, precluding the ability to do multiplicity adjustments or to adjust for centre effects. To limit the effect of multiplicity, the efficacy results are presented in terms of estimated changes and corresponding 95% CIs and *p* values are considered as nominal. Standardised methods for spirometry and sweat collection were used, which should reduce the centre effect or variability owing to centre. In addition, these studies enrolled a small number of participants from marginalised groups. There are several factors that contribute to the disproportionate under-enrolment of people with cystic fibrosis from marginalised groups. In marginalised individuals, the *F508del*-CFTR mutation is less common and these individuals have a higher likelihood of having an

unknown CFTR mutation or a deletion or duplication that could be missed on a DNA panel.¹⁹ Additionally, participation in clinical trials might also be more challenging for marginalised individuals owing to barriers such as mistrust of the medical community, lack of comfort and information on the clinical trial process, time and resource constraints, and lack of trial awareness.²⁰

The safety profile and efficacy of vanzacaftor–tezacaftor–deutivacaftor observed in these phase 2 studies justify proceeding to phase 3 clinical trials. The design of future CFTR modulator trials for people with cystic fibrosis and at least one *F508del* allele, especially in those already receiving efficacious therapies, such as elexacaftor–tezacaftor–ivacaftor, presents several challenges. First, studies will need to compare any new regimen against elexacaftor–tezacaftor–ivacaftor so as to evaluate the benefit–risk against the existing standard of care for cystic fibrosis treatment. Second, resolving differences between effective therapies might require larger sample sizes and longer treatment durations compared with placebo. Lastly, investigators will need to carefully consider the acceptability of discontinuing modulator treatment in stable patients, as such discontinuation might lead to clinical deterioration. Overall, any new therapy will have to show the potential to be at least as effective as, or more effective than, elexacaftor–tezacaftor–ivacaftor.²¹ Consistent with these points, the phase 3 programme for vanzacaftor–tezacaftor–deutivacaftor consists of two randomised, double-blind, active-controlled, 52-week trials evaluating the efficacy and safety of vanzacaftor–tezacaftor–deutivacaftor in comparison with elexacaftor–tezacaftor–ivacaftor. The first study will enrol approximately 400 patients with cystic fibrosis aged 12 years or older with *F/MF* genotypes (NCT05033080). The second study will enrol approximately 550 patients with cystic fibrosis aged 12 years or older with the *F/F* genotype or one *F508del* mutation and a second mutation responsive to CFTR modulators or at least one other triple combination responsive CFTR mutation and no *F508del* mutation (NCT05076149). The primary endpoint in both studies is the absolute change from baseline in ppFEV₁, which will be analysed for non-inferiority to elexacaftor–tezacaftor–ivacaftor. Both studies will also assess absolute change from baseline in ppFEV₁ and sweat chloride concentration for superiority to elexacaftor–tezacaftor–ivacaftor.

The current studies show that vanzacaftor in triple combination with tezacaftor and deutivacaftor is efficacious in adults with cystic fibrosis who have *F/MF* or *F/F* genotypes. Vanzacaftor–tezacaftor–deutivacaftor was safe and well tolerated, with most participants having adverse events that were mild or moderate in severity and generally consistent with manifestations of cystic fibrosis. The favourable benefit–risk profile showed in these studies, along with the potential for vanzacaftor–tezacaftor–deutivacaftor to be superior to

elxacaftor–tezacaftor–ivacaftor in restoring CFTR function, support the further investigation of vanzacaftor–tezacaftor–deutivacaftor in phase 3 trials against elxacaftor–tezacaftor–ivacaftor, the standard-of-care treatment for cystic fibrosis.

Contributors

The study sponsor (Vertex Pharmaceuticals) designed the protocol for the studies in collaboration with the authors. Site investigators collected the data, which were analysed by the sponsor. The data were verified by NN, CC, and YX. All authors had full access to the study data and provided input on drafting the manuscript, with writing assistance from the sponsor. All authors participated in subsequent revisions of the manuscript and approved the final version submitted for publication. Medical writing support, provided by the funder of the study, was done at the direction and guidance of the authors.

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.

Declaration of interests

AZU received grants from the Cystic Fibrosis Foundation and the CFF-Therapeutic Development Network for the present work; received payment or honoraria from Vertex Pharmaceuticals for presentations at CF Centers in UK; and participated in advisory boards for Vertex and Eloxx. VI received grant support from CF TDN for the present work; consulting fees from Mylan for CF—TOBI podhaler advisory board; and grant support from CFF for meeting attendance. PA received support from Vertex Pharmaceuticals for lectures, presentations, and materials; meeting attendance; and participation on data safety monitoring boards or advisory boards. MAM received payment from Vertex for the current work and personal fees for serving on an advisory board; grants from Vertex and from the German Ministry for Education and Research; consulting fees from Boehringer Ingelheim, Arrowhead Pharmaceuticals, Vertex Pharmaceuticals, Santhera, Sterna Biologicals, Enterprise Therapeutics, Antabio, and Abbvie; lecture fees from Boehringer Ingelheim, Arrowhead Pharmaceuticals, and Vertex Pharmaceuticals; travel reimbursement from Boehringer Ingelheim and Vertex Pharmaceuticals; personal fees for participation in an advisory board from Boehringer Ingelheim, Arrowhead Pharmaceuticals, Vertex Pharmaceuticals, Santhera, Enterprise Therapeutics, Antabio, Kither Biotech, Abbvie, and Pari; and serves as an ECFS Board member. EFM received grants and other payments or honoraria from Vertex; and support for meetings or travel from Menarini. BWR received payments from Vertex for the present work, and payments for a presentation in Vancouver, BC, Canada in 2019; and participated on data safety monitoring boards or advisory boards for CF Storm Clinical Trial, Vertex Pharmaceuticals, Janssen, Abbvie, and Insmed. SMR received support for a clinical trial; consulting fees on the design and conduct of clinical trials; support for meeting attendance and for his role as Co-Chair of the Next Generation Steering Committee; received grants or contracts from Novartis, TranslateBio, Galapagos–Abbvie, Synedgen–Synspira, Eloxx, Vertex Pharmaceuticals, and Ionis Astra Zenica; consulting fees from Novartis, Galapagos–Abbvie, Synedgen–Synspira, Vertex Pharmaceuticals, Renovion, Ionis, Cystetic Medicines, and Arcturus; support for meeting attendance from Vertex; has patents planned, issued or pending; serves as a Co-Chair of the Next Generation Steering Committee; and owns stock or stock options with Synedgen–Synspira and Renovion. RCR received clinical trial support and consulting fees from Vertex for the present work; grants from CFF, NIDDK, NHLBI, NICHHD, and NIDCD; received consulting fees from Guidepoint Global, Gerson Lehrman Group, and Cystic Fibrosis Foundation; participated on a data safety monitoring or advisory board for NHLBI DSMB. JLT-C received personal consulting fees from Vertex for the present work; received grants from Vertex, Eloxx, and 4DMT for the conduct of a research trial; personal fees from Vertex, Insmed, and 4DMT for trial design consulting; personal

fees from Vertex for non-branded speaking; and personal fees from AbbVie for her role as DMC Chair; served as the adult patient care representative to the CFF Board of Trustees, on the CF Foundation's Clinical Research Executive Committee, Clinical Research Advisory Board, and Racial Justice Working Group; as immediate past chair of the CF TDN's Sexual Health, Reproduction and Gender Research Working Group; on the scientific advisory board for Emily's Entourage; on the ATS Respiratory Health Awards Working Group; on the ATS Scientific Grant Review and Clinical Problems Assembly Programming Committees; and served as an associate editor for the *Journal of Cystic Fibrosis*. ET received payment for the present work and grants for doing clinical trials from Vertex Pharmaceuticals; received payment and reimbursement from Vertex for her role on a steering committee and for presentations at educational events. JB received funding from Vertex Pharmaceuticals for the present work. AH received funding from Vertex Pharmaceuticals for the present work; grant support from NIHR, CF Trust, CF Foundation, and Medical Research Council; payments for educational lectures from Vertex Pharmaceuticals and for an advisory board from Mylan; medical writing support from Vertex; served as Chair of the UK CF Clinical Trials Accelerator Platform and as a board member of the UK CF Medical Association. LMY received salary support from mgH TDN for clinical research activity for the present work. DW has patents planned, issued or pending. DW, LTW, CC, APM, NN, PRS, ST, FVG, and YX are Vertex employees and might own stocks or stock options. GM and CK have nothing to disclose. LV was a clinical pharmacology lead at Vertex during the conduct of this study and conducted PK data analysis for the present study.

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