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Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two *F508del* alleles

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ABSTRACT Cystic fibrosis (CF) is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*) that result in diminished quantity and/or function of the CFTR anion channel. *F508del-CFTR*, the most common CF-causing mutation (found in ~90% of patients), causes severe processing and trafficking defects, resulting in decreased CFTR quantity and function. CFTR modulators are medications that increase the amount of mature CFTR protein (correctors) or enhance channel function (potentiators) at the cell surface.

Combinations of CFTR correctors and potentiators (*i.e.* lumacaftor/ivacaftor, tezacaftor/ivacaftor) have demonstrated clinical benefit in subsets of patients. However, none are approved for patients with CF heterozygous for *F508del*-CFTR and a minimal function mutation, *i.e.* a mutation that produces either no protein or protein that is unresponsive to currently approved CFTR modulators. Next-generation CFTR correctors VX-659 and VX-445, each in triple combination with tezacaftor and ivacaftor, improve CFTR processing, trafficking and function *in vitro* and have demonstrated clinical improvements in phase 2 studies in patients with CF with one or two *F508del-CFTR* alleles.

Here, we present the rationale and design of four randomised phase 3 studies, and their open-label extensions, evaluating VX-659 (ECLIPSE) or VX-445 (AURORA) plus tezacaftor and ivacaftor in patients with one or two *F508del-CFTR* alleles.

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An efficient development programme for VX-659 and VX-445 in triple combination with tezacaftor/ivacaftor in patients with CF with one or two *F508del-CFTR* alleles was designed based on extensive CFTR modulator experience and pre-clinical and clinical data. http://bit.ly/2UBh6EV

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This article does not report study data, but provides the rationale and study design for two comprehensive phase 3 development programmes (ECLIPSE and AURORA): ClinicalTrials.gov identifiers NCT03447249, NCT03460990, NCT03447262, NCT03525444, NCT03525548 and NCT03525574.

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Introduction

Cystic fibrosis (CF) is a rare, severe, multisystem disease affecting more than 80 000 people worldwide [1]. CF is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*) that lead to defects in the CFTR protein [2]. CFTR is an ion channel that regulates the transport of chloride and bicarbonate at the cell surface [2–4]. Mutations in CFTR disrupt the activity of the protein by reducing its quantity or function [5]. Clinical manifestations of CF include chronic endobronchial infections, decreased lung function, malnutrition, exocrine pancreatic insufficiency, CF-related diabetes and reduced life expectancy [6]. Approximately 90% of patients with CF carry one or more copies of the *F508del-CFTR* mutant allele [7], which results in decreased quantity and function of CFTR protein at the cell surface [8].

Based on an understanding of the molecular defects caused by the *F508del-CFTR* mutation, CFTR modulators that increase the quantity and/or enhance the function of CFTR protein at the cell surface were developed [9–13]. The history of CFTR modulator development was recently reviewed [5]. The systemic delivery of CFTR modulators translates into clinical improvements in multiorgan CF manifestations, including lung function, nutritional status, pulmonary exacerbations and quality of life [14–17]. The first available modulator was the CFTR potentiator ivacaftor (IVA), which augments anion transport by increasing CFTR channel-open probability [9]. IVA monotherapy is approved in selected regions for the treatment of patients with CF with *CFTR* mutations that produce cell surface-localised CFTR that is responsive to the potentiator, including gating mutations and mutations with residual CFTR function [18–20]. Lumacaftor (LUM) and tezacaftor (TEZ) are CFTR correctors that augment intracellular F508del-CFTR processing and trafficking, thereby increasing the amount of mature CFTR at the cell surface [10–12]. LUM and TEZ, each in combination with IVA, have shown clinical benefit and are indicated in selected regions in patients with CF homozygous for *F508del-CFTR* (*F508del*/*F508del*); TEZ/IVA therapy is also indicated in selected regions in patients with CF heterozygous for *F508del-CFTR* and a CFTR mutation that is responsive to TEZ/IVA, based on *in vitro* and/or clinical data [21–24].

Despite the availability of CFTR modulator therapies for many patients with CF, there are no approved CFTR modulators to treat the estimated 30% of patients with CF heterozygous for *F508del-CFTR* and a minimal function (MF) mutation, defined as a mutation that does not produce protein (*e.g.* the *CFTR* nonsense mutation *G542X*) or produces protein that is unresponsive to TEZ, IVA and the combination of TEZ/IVA (*e.g.* the *CFTR* missense mutation *N1303K*, which results in a severe processing defect) [1, 25]. Furthermore, although TEZ/IVA and LUM/IVA are efficacious in individuals with the *F508del*/*F508del* genotype, the magnitude of clinical benefit is not as marked as that experienced by patients with gating mutations treated with IVA, the benchmark of highly effective CFTR modulation [14–16, 26]. We therefore built on the molecular understanding of F508del-CFTR to develop next-generation CFTR correctors that restore high levels of F508del-CFTR activity when used in triple combination with TEZ/IVA in patients with *F508del*/MF genotypes, who have a single responsive *F508del-CFTR* allele; the strategy is also intended to maximise CFTR activity in patients with the *F508del*/*F508del* genotype. Achievement of these goals was successfully demonstrated in phase 2 trials testing two distinct triple-combination regimens (VX-659/TEZ/IVA and VX-445/TEZ/IVA) in patients with *F508del*/*F508del* and *F508del*/MF genotypes [25, 27]. The studies described herein are designed to validate these early clinical results in a larger group of patients with CF and can potentially bring a next-generation corrector in triple combination with TEZ/IVA to patients with CF with one or two *F508del-CFTR* alleles, representing significant clinical progress in up to 90% of the population of patients with CF.

Rationale

The *F508del-CFTR* mutation exhibits multiple molecular defects, including defective cell processing, reduced stability at the cell surface and diminished channel gating [28]. Single-drug correction of cellular misprocessing such as occurs with F508del-CFTR is particularly challenging because multiple intracellular checkpoints exist to remove unstable proteins [5]. VX-659 and VX-445 are next-generation correctors with a different structure and mechanism of action than the first-generation correctors TEZ and LUM [25, 27, 29]. *In vitro* work in human bronchial epithelial (HBE) cells isolated from patients with CF with *F508del*/MF or *F508del*/*F508del* genotypes demonstrated that a combination of correctors with different mechanisms of action (*e.g.* TEZ and VX-659 or VX-445) can work additively through complementary mechanisms of action to increase the amount of F508del-CFTR at the cell surface to a higher level than any single corrector [25, 27, 29]. Additionally, triple-combination regimens with next-generation correctors increased *in vitro* CFTR function to a greater degree than did any dual combination of CFTR modulators [25, 27]. The level of CFTR modulation achieved by these triple-combination treatments in HBE cells with one or two *F508del-CFTR* alleles met or exceeded the high standard set by IVA in HBE cells expressing *G551D-CFTR* (~50% of wild-type CFTR function) [9, 25, 27]. Importantly, the *in vitro* results observed following IVA treatment in HBE cells expressing *G551D-CFTR* translated into short- and long-term improvements in clinical outcome in patients with *G551D-CFTR* mutations treated with IVA

(*i.e.* significant improvements in lung function, nutritional status and patient-reported outcomes), consistent with modification of the underlying disease [9, 14, 30–33]. The pre-clinical and clinical experience with IVA suggests that triple combinations can potentially provide similar levels of clinical efficacy for patients homozygous for *F508del-CFTR* or heterozygous for *F508del-CFTR* and an MF mutation [29].

Using an approach unprecedented in scope and breadth in CF clinical research, four novel next-generation correctors (VX-152, VX-440, VX-445 and VX-659) were concurrently evaluated in triple combination with TEZ/IVA in phase 1 and 2 studies in patients with *F508del*/MF or *F508del*/*F508del* genotypes to assess pharmacokinetics, safety and early evidence of efficacy [25, 29]. Four next-generation correctors were evaluated because there is an important medical need, the potential to realise benefit based on prior *in vitro* and clinical experience was strong, and the inherent risk of drug development is high (including the potential to identify unanticipated toxicity) [25]. TEZ/IVA was chosen as the backbone for the triple-combination regimens because of favourable pharmacological properties, including lack of cytochrome P450 3A induction [16, 17, 34]. To further mitigate risk, initial studies of triple combinations included selected short-term testing in patients with CF after initial safety and pharmacokinetic testing in healthy volunteers (EudraCT trials 2016-003048-35 and 2017-000797-11; ClinicalTrials.gov identifiers NCT03029455 and NCT03227471).

Although all four triple combinations demonstrated preliminary evidence of clinical benefit [25, 27, 35] that was relatively similar in magnitude, two next-generation compounds (VX-659 and VX-445) showed high levels of efficacy together with safety profiles and pharmacological properties suitable for long-term use, and they were selected for further development in phase 3 programmes. VX-659 and VX-445 in triple combination with TEZ/IVA were evaluated in phase 2, randomised, controlled studies in patients with *F508del*/*F508del* and *F508del*/MF genotypes. Different comparator arms were required for each group. For patients with the *F508del*/*F508del* genotype, the approved CFTR modulator TEZ/IVA was the comparator and the baseline (following a 4-week run-in period) for within-group changes. The comparator for patients with *F508del*/MF genotypes was placebo because there is no approved CFTR modulator available for these patients. In these phase 2 studies, VX-659/TEZ/IVA and VX-445/TEZ/IVA demonstrated clinically significant improvements in lung function as measured by the absolute change from baseline in forced expiratory volume in 1 s (FEV_1) % pred through 4 weeks of treatment in patients with *F508del*/MF genotypes (within-group increases from baseline of up to 13.3 and 13.8 percentage points, respectively) and the *F508del*/*F508del* genotype (within-group increases from baseline of 9.7 and 11.0 percentage points beyond effects with TEZ/IVA, respectively) (figure 1) [25, 27]. In each case, as with other CFTR modulators, the vast majority of FEV_1 % pred responses were present at 2 weeks [14–17], indicating that the improvements in lung function occurred rapidly. VX-659 and VX-445 triple combinations also reduced (*i.e.* improved) sweat chloride concentrations, an important *in vivo* pharmacodynamic biomarker of CFTR function, in patients with *F508del*/MF genotypes (within-group decreases from baseline up to −51.4 and −39.1 $mmol \cdot L^{-1}$, respectively) and the *F508del*/*F508del* genotype (within-group decreases from baseline of −42.2 and −39.6 $mmol \cdot L^{-1}$ beyond effects with TEZ/IVA, respectively) [25, 27]. Improvements in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain scores (for which the established minimal clinically important difference is 4.0 points) [36] were also robust with VX-659 and VX-445 triple combinations (within-group change from baseline up to 24.6 and 25.7 points in the *F508del*/MF cohorts; within-group change from baseline of 19.5 and 20.7 points beyond effects with TEZ/IVA in the *F508del*/*F508del* cohorts, respectively) and compared favourably with those observed in prior CFTR modulator studies. VX-659 and VX-445 triple combinations had acceptable safety profiles over 4 weeks, with the majority of adverse events being mild or moderate [25, 27]. These phase 2 proof-of-concept studies demonstrated that targeting the F508del-CFTR protein with a triple-combination regimen containing two complementary correctors and a potentiator can restore substantial CFTR function, even in patients with a single *F508del-CFTR* allele, leading to clinically significant improvements in lung function [25, 27]. Indeed, the magnitude of response with these triple-combination regimens exceeded the benchmark of robust improvement in CFTR modulation set by IVA in patients with a *G551D-CFTR* mutation [14, 25, 27].

These highly promising phase 2 results led to the advancement of VX-659 and VX-445 triple combinations to parallel phase 3 development programmes (ECLIPSE and AURORA, respectively). Together, the ECLIPSE and AURORA programmes represent one of the largest phase 3 CFTR modulator development programmes ever conducted in CF. The programmes were informed by previous experience with CFTR modulators, incorporating efficient study designs to rapidly identify a triple-combination regimen suitable as a new treatment option for patients with one or two *F508del-CFTR* mutations.

Each programme includes separate pivotal studies in patients with the *F508del*/MF and *F508del*/*F508del* genotypes. This approach is necessary because the standard of care is different in these two populations

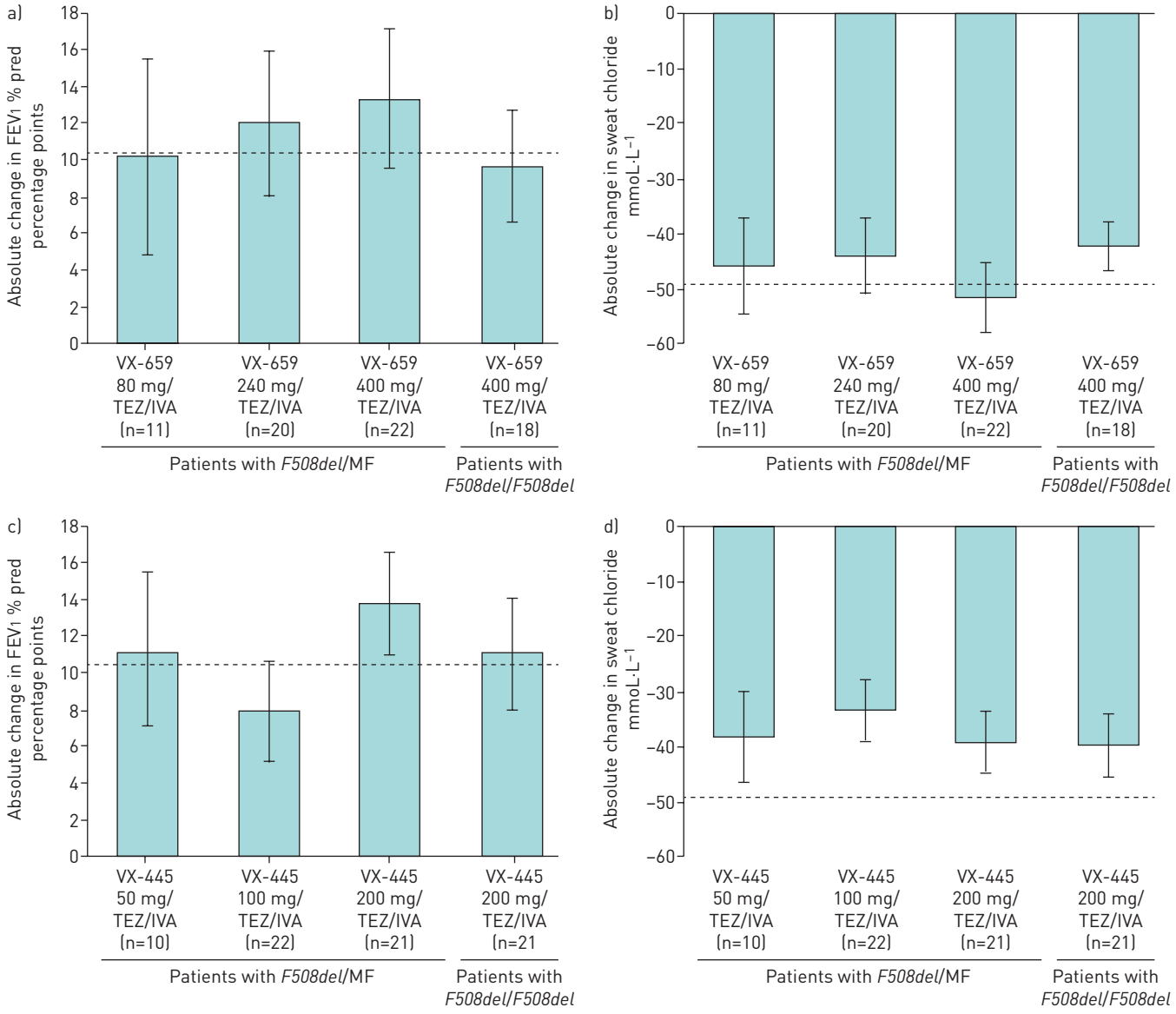

FIGURE 1 Summary of absolute changes from baseline in a, c) forced expiratory volume in 1 s (FEV1) % pred and b, d) sweat chloride concentration after triple-combination treatment for 4 weeks with a, b) VX-659/tezacaftor (TEZ)/ivacaftor (IVA) or c, d) VX-445/TEZ/IVA in patients with *F508del*/minimal function (MF) or *F508del*/*F508del* genotypes evaluated in phase 2 studies [25, 27]. Patients with *F508del*/*F508del* received TEZ/IVA during a 4-week run-in period, thus absolute changes in this group were in addition to changes with TEZ/IVA alone. Dotted lines indicate absolute change from baseline in a, c) FEV1 % pred (10.4 percentage points) and b, d) sweat chloride concentration (−48.7 mmol·L^{-1}) through week 24 with IVA in patients with a *G551D* mutation [14]. 95% confidence intervals are indicated.

[25, 27] and, as mentioned earlier, they require different comparator groups (placebo plus TEZ/IVA for patients with the *F508del*/*F508del* genotype; placebo for patients with *F508del*/MF genotypes).

The studies in patients with *F508del*/MF genotypes (VX17-659-102 and VX17-445-102) serve as the placebo-controlled anchor studies for their respective triple-combination programmes. These are 24-week studies that will assess both short- and longer-term changes in lung function as well as longer-term changes in pulmonary exacerbations and nutritional status. The primary end-point is the absolute change in FEV1 % pred from baseline, assessed at week 4 (global protocol) and through week 24 (European protocol). These studies in patients with *F508del*/MF genotypes are also powered to assess the change in pulmonary exacerbation rates from baseline through week 24. Because studies in patients with the *F508del*/*F508del* genotype already receiving TEZ/IVA would require prohibitively large patient numbers (more than 1500 patients each) to be sufficiently powered to detect 30% reductions in pulmonary exacerbations over a 24-week treatment period, studies in patients with *F508del*/MF genotypes provide a unique opportunity to effectively assess pulmonary exacerbation rates in both the ECLIPSE and AURORA programmes.

Importantly, experience with approved CFTR modulators across multiple studies has shown that the safety profile of CFTR modulators is independent of *CFTR* genotype; therefore, the studies in patients with *F508del*/MF genotypes will provide placebo-controlled safety data applicable to both *F508del*/MF and *F508del*/*F508del* populations.

The studies in patients with the *F508del*/*F508del* genotype (VX17-659-103 and VX17-445-103) are 4 weeks in duration and powered to assess the primary end-point of absolute change in FEV_1 % pred from baseline at week 4. The 4-week time-point was selected for evaluation of lung function across all studies because experience with the approved CFTR modulators IVA, LUM/IVA and TEZ/IVA has consistently shown that the absolute change in FEV_1 % pred from baseline at 4 weeks predicts durable improvements in lung function, as illustrated by longitudinal plots showing the mean absolute change from baseline in FEV_1 % pred through 24 to 48 weeks in representative phase 3 studies (figure 2). In all representative studies, there was rapid separation (*i.e.* by day 15) between the FEV_1 % pred curves for the active treatment and placebo groups that was sustained [14–17, 37]. This rapid effect and the ability of short-term outcomes to predict long-term effects has been observed across groups of patients with different genotypes, baseline FEV_1 % pred and age [14–17, 30, 37–39]. Importantly, lung function and other efficacy outcomes observed with approved CFTR modulators in pivotal trials have been sustained during long-term use [40, 41].

Long-term safety and efficacy will be assessed in the ECLIPSE and AURORA programmes through compound-specific 96-week open-label extension studies made available to patients following their completion of the randomised placebo-controlled (*F508del*/MF) or active-controlled (*F508del*/*F508del*) treatment studies.

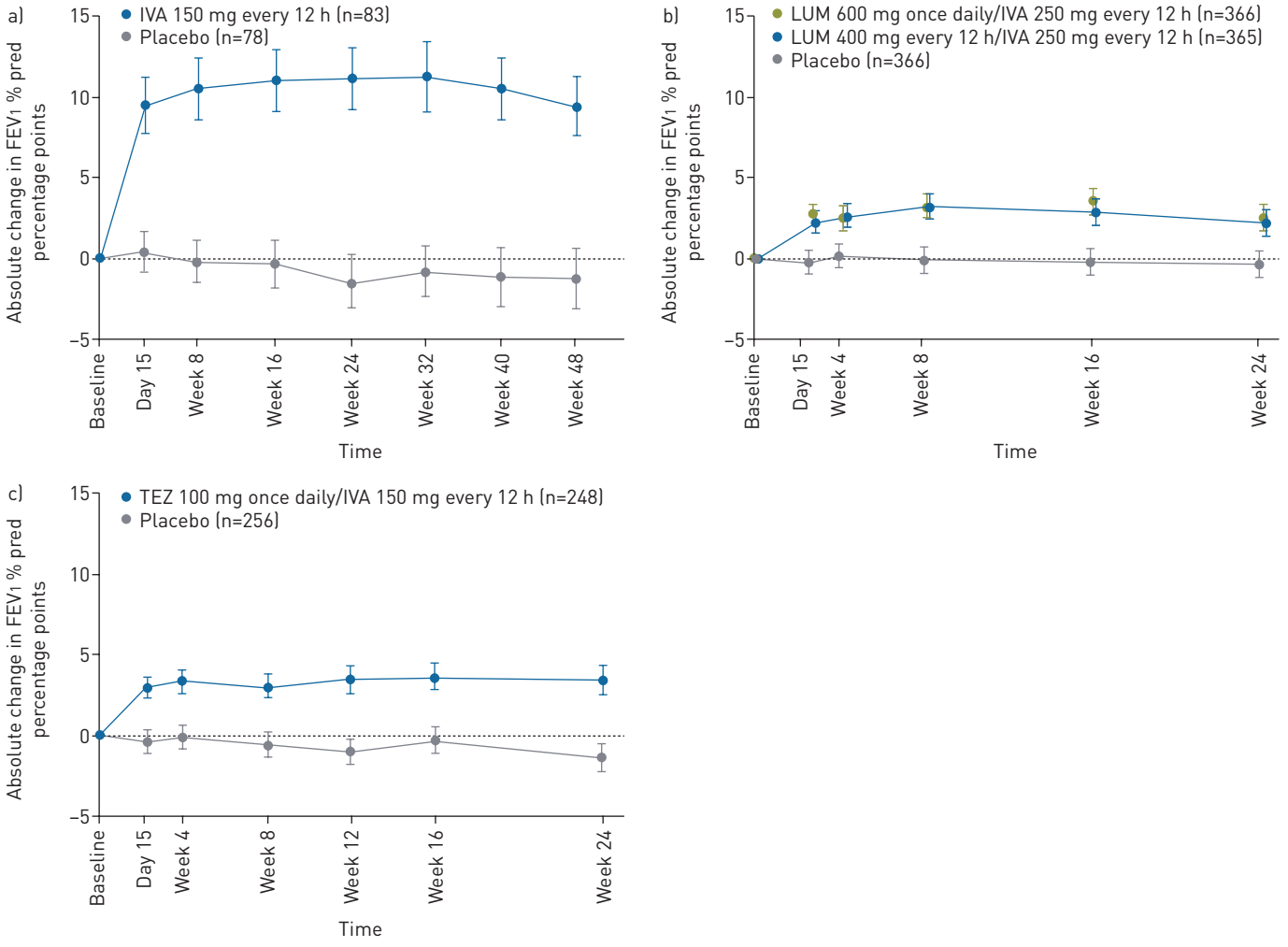

FIGURE 2 Absolute change in forced expiratory volume in 1 s (FEV_1) % pred over time in clinical trials with a) ivacaftor (IVA) in patients with at least one *G551D* allele [14], b) lumacaftor (LUM)/IVA in patients with the *F508del*/*F508del* genotype [15] and c) tezacaftor (TEZ)/IVA in patients with the *F508del*/*F508del* genotype [16]. Reproduced from [14–16] with permission.

Methods

Randomised controlled studies: VX17-659-102, VX17-445-102, VX17-659-103 and VX17-445-103

Study design and participants

VX17-659-102 and VX17-445-102 are two identically designed randomised, double-blind, placebo-controlled studies evaluating the efficacy and safety of VX-659 (VX17-659-102; ClinicalTrials.gov identifier NCT03447249) or VX-445 (VX17-445-102; ClinicalTrials.gov identifier NCT03525444) in triple combination with TEZ/IVA in patients with CF with *F508del*/MF genotypes (figure 3a) as previously defined [25, 27]. Mutations that are considered MF based on *in vitro* testing have baseline chloride transport that is <10% of wild-type CFTR and increases <10% over baseline after the addition of TEZ, IVA or TEZ/IVA [25, 42]. These studies were each planned to randomise approximately 360 patients (1:1) to triple combination (active treatment) or placebo (n=180 per group) for 24 weeks.

VX17-659-103 and VX17-445-103 are two identically designed randomised, double-blind studies evaluating the efficacy and safety of VX-659 (VX17-659-103; ClinicalTrials.gov identifier NCT03460990) or VX-445 (VX17-445-103; ClinicalTrials.gov identifier NCT03525548) in triple combination with TEZ/IVA compared with TEZ/IVA alone in patients with CF with the *F508del/F508del* genotype (figure 3b). These studies were each planned to randomise approximately 100 patients (1:1) to triple combination or TEZ/IVA (n=50 per group) for 4 weeks.

All studies include male and female patients aged ⩾12 years with mild to moderate stable CF (FEV_1 % pred ⩾40% and ⩽90% at screening). Additional inclusion and exclusion criteria are listed in table 1.

All studies include a 4-week screening period, a treatment period and a 4-week safety follow-up period for patients not proceeding to an open-label study. The regimen administered during the treatment period includes triple combination with VX-659 (240 mg once daily) or VX-445 (200 mg once daily) plus the

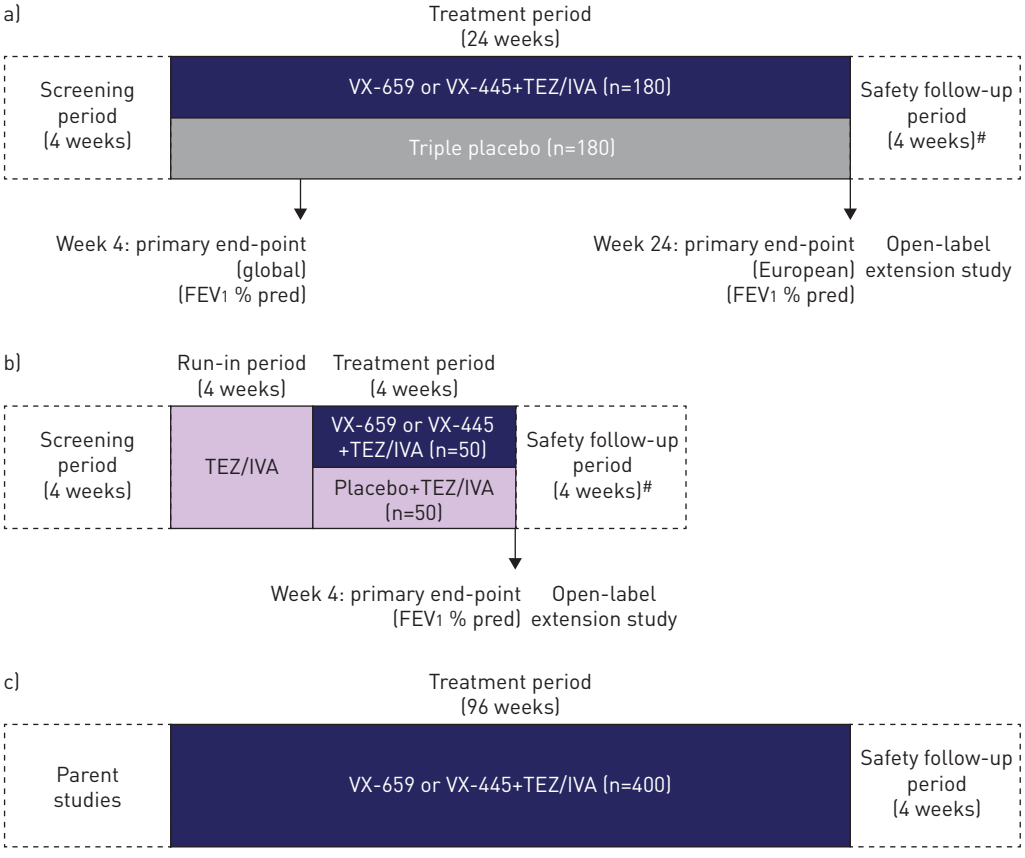

FIGURE 3 Study design for ECLIPSE (VX-659 triple combination) and AURORA (VX-445 triple combination) phase 3 studies. TEZ: tezacaftor; IVA: ivacaftor; FEV_1: forced expiratory volume in 1 s. a) Randomised controlled studies in patients with *F508del*/minimal function genotypes: VX17-659-102 (n~360) and VX17-445-102 (n~360). b) Randomised controlled studies in patients with the *F508del/F508del* genotype: VX17-659-103 (n~100) and VX17-445-103 (n~100). c) Open-label extension studies: VX17-659-105 (n~400) and VX17-445-105 (n~400). All sample sizes are per study. #: the 4-week safety follow-up visit in the parent studies is required only for patients who do not proceed to the open-label extension studies.

TABLE 1 Key inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Randomised controlled studies: VX17-659-102, VX17-445-102, VX17-659-103 and VX17-445-103		
Sex	Male or female	Pregnant or nursing female
Age years	⩾12	<12
CFTR genotype	*F508del*/MF; *F508del*/*F508del*	All other genotypes
Disease status	Stable CF disease; FEV_1 % pred ⩾40% and ⩽90%	Acute respiratory infection, pulmonary exacerbations or changes in therapy for sinopulmonary disease[#]
Concomitant medications	Willingness to remain on a stable CF treatment regimen	Use of restricted medications within the specified window before the first dose of study drug[¶]
Consent	Written informed consent	NA
Open-label extension studies: VX17-659-105 and VX17-445-105		
Parent study	Completion of study drug treatment or interruption of study drug but with subsequent completion of the parent study	Drug intolerance in a parent study that, in the opinion of the investigator, would pose an additional risk to the patient; current participation in an investigational drug trial (other than a parent study)

CFTR: cystic fibrosis transmembrane conductance regulator; MF: minimal function; FEV_1: forced expiratory volume in 1 s; NA: not applicable; CYP3A: cytochrome P450 3A. [#]: within 28 days before the first dose of study drug; [¶]: restricted medications within 14 days of the first dose of study drug include moderate and strong CYP3A inducers, moderate and strong CYP3A inhibitors, and sensitive organic anion transporting polypeptide 1B1 substrates.

approved commercial dose of TEZ (100 mg once daily) and IVA (150 mg every 12 h), or matched placebo control (triple placebo in the *F508del*/MF cohorts or placebo plus TEZ/IVA in the *F508del*/*F508del* cohorts). Patients with the *F508del*/*F508del* genotype receive TEZ/IVA during a 4-week run-in period to maintain standard-of-care therapy and to provide a reliable baseline to assess the benefit of adding a second CFTR corrector to TEZ/IVA. All study drugs are administered orally. Scheduled clinical, laboratory and safety assessments are listed in tables 2 and 3.

Randomisation and masking

Patients are randomised 1:1 after screening (*F508del*/MF genotypes) or after the TEZ/IVA run-in (*F508del*/*F508del* genotype). Patients are stratified by FEV_1 % pred (<70% *versus* ⩾70%) and age (<18 *versus* ⩾18 years); patients with *F508del*/MF genotypes are also stratified by sex (male *versus* female). Treatment is assigned with an interactive web-based response system and is blinded for all patients, caregivers, investigators, site personnel and the sponsor (*i.e.* the study team).

TABLE 2 Treatment periods and safety follow-up visits: randomised controlled studies in patients with *F508del*/MF genotypes: VX17-659-102 and VX17-445-102

Event/assessment	Day 1	Day 15	Week 4	Week 8	Week 12	Week 16	Week 24	ETT visit[#]	Safety follow-up[¶]
Clinic visit[+]	+	+	+	+	+	+	+	+	+
CFQ-R[§]	+	–	+	+	+	+	+	+	+
Weight and height[f]	+	+	+	+	+	+	+	+	+
Spirometry	+	+	+	+	+	+	+	+	+
Sweat chloride concentration	+	–	+	+	+	–	+	+	–
Haematology/serum chemistry	+	+	+	+	+	+	+	+	+
Pharmacokinetics sampling	+	–	+	+	+	+	–	+	–
Study drug count	+	+	+	+	+	+	+	+	–
AEs and SAEs[##]	+	+	+	+	+	+	+	+	+

MF: minimal function; ETT: early termination of treatment; CFQ-R: Cystic Fibrosis Questionnaire-Revised; AE: adverse event; SAE: serious AE. [#]: an ETT visit should be scheduled as soon as possible if a patient prematurely discontinues study treatment. [¶]: 28±7 days after the last dose of study drug (if applicable). [+]: additional telephone contact at week 20. [§]: the CFQ-R must be completed before any other assessment. In these randomised controlled studies the CFQ-R is followed by the Treatment Satisfaction Questionnaire for Medication (patients aged ⩾12 to <18 years at the date of informed consent); remaining assessment may be performed in any order when more than one assessment is required at a particular clinic visit. [f]: weight and height will be measured with shoes off. Following screening, height will be collected only for subjects ⩽21 years of age on the date of informed consent. [##]: AEs and SAEs continuously assessed through completion of study participation.

TABLE 3 Treatment periods and safety follow-up visits: randomised controlled studies in patients with the *F508del/F508del* genotype: VX17-659-103 and VX17-445-103

Event/assessment	TEZ/IVA run-in		Day 1	Day 15	Week 4	ETT visit[#]	Safety follow-up[¶]
	Day −28	Day −14					
Clinic visit	+	+	+	+	+	+	+
CFQ-R[+]	–	–	+	+	+	+	+
Weight and height[§]	+	–	+	+	+	+	+
Spirometry	–	+	+	+	+	+	+
Sweat chloride concentration	–	+	+	+	+	+	–
Haematology/serum chemistry	+	–	+	+	+	+	+
Pharmacokinetics sampling	–	–	+	–	+	+	–
Study drug count	–	–	+	+	+	+	–
AEs and SAEs[f]	+	+	+	+	+	+	+

TEZ: tezacaftor; IVA: ivacaftor; ETT: early termination of treatment; CFQ-R: Cystic Fibrosis Questionnaire-Revised; AE: adverse event; SAE: serious AE. [#]: an ETT visit should be scheduled as soon as possible if a patient prematurely discontinues study treatment. [¶]: 28±7 days after the last dose of study drug (if applicable). [+]: the CFQ-R must be completed before any other assessment. In these randomised controlled studies the CFQ-R is followed by the Treatment Satisfaction Questionnaire for Medication (patients aged ⩾12 to <18 years at the date of informed consent); remaining assessment may be performed in any order when more than one assessment is required at a particular clinic visit. [§]: weight and height will be measured with shoes off. Following screening, height will be collected only for subjects ⩽21 years of age on the date of informed consent. [f]: AEs and SAEs continuously assessed through completion of study participation.

Study end-points

The primary objective of each study is to evaluate the efficacy of VX-659 or VX-445 in triple combination with TEZ/IVA in patients with CF with *F508del*/MF or *F508del*/*F508del* genotypes. In the global protocols, the primary end-point in patients with *F508del*/MF and *F508del*/*F508del* genotypes is absolute change in FEV_1 % pred from baseline at week 4. In the European protocol, the primary end-point in patients with *F508del*/MF genotypes is absolute change in FEV_1 % pred from baseline through week 24. Key secondary and other end-points are listed in table 4.

Statistical analyses

The absolute change from baseline in FEV_1 % pred at week 4 will be evaluated in all studies, with the change through week 24 also evaluated in studies in patients with *F508del*/MF genotypes. These end-points will be analysed using a mixed effects model for repeated measures (MMRM) with change from baseline in FEV_1 % pred as the dependent variable. The model will include treatment group, visit and treatment-by-visit interaction as fixed effects, with continuous baseline FEV_1 % pred and age (<18 *versus* ⩾18 years) as covariates; sex (female *versus* male) will be included as a covariate in studies in patients with *F508del*/MF genotypes, and the model will use an unstructured covariance for the within-subject errors. The MMRM model has been used successfully throughout much of the CFTR modulator development programme and provides advantages such as evaluating a treatment effect throughout the study period, handling for missing data and reducing bias [43].

In the 24-week studies in patients with *F508del*/MF genotypes, an interim analysis of efficacy (including absolute change from baseline in FEV_1 % pred) and safety is planned after 140 or more patients complete the week 4 visit and 100 or more patients complete the week 12 visit, permitting the option for accelerated regulatory submissions in selected regions. A Lan–DeMets α spending function will be applied to control the overall type I error rate of 0.05 for the 4-week end-point during the interim analysis and the final analysis, such that an α of 0.01 will be preserved for the final analysis [44]. If the number of patients included in the interim analysis is 140, then the absolute change from baseline in FEV_1 % pred at week 4 will be tested at a significance level of 0.044 during the interim analysis. The actual α at the interim analysis (α_0) will be determined based on the actual number of patients included in the interim analysis. Assuming a within-group standard deviation of 7 percentage points and a 5% dropout rate at week 4, an interim analysis sample size of 70 patients in each treatment group will have ~98% power to detect a difference of 5 percentage points between the treatment groups, based on a two-sided, two-sample t-test at a significance level of 0.044. Regardless of the outcome of the interim analysis, the study will remain blinded, and all patients will continue through the 24-week treatment period.

Approximately 360 patients with *F508del*/MF genotypes per study were determined to provide adequate power to detect a difference in the number of pulmonary exacerbation events between triple combination and placebo through week 24. Assuming a pulmonary exacerbation rate of 0.6 for the triple-placebo groups

TABLE 4 Study end-points

Randomised controlled studies: VX17-659-102, VX17-445-102, VX17-659-103 and VX17-445-103

Primary end-point

F508del/MF genotypes (VX17-659-102 and VX17-445-102): absolute change in FEV_1 % pred from baseline at week 4 (global protocol); through week 24 (European protocol)

F508del/*F508del* genotype (VX17-659-103 and VX17-445-103): absolute change in FEV1 % pred from baseline at week 4

Key secondary end-points

Absolute change in FEV_1 % pred from baseline through week 24 (global protocol) and at week 4 (European protocol)#

Number of pulmonary exacerbation events through week 24#

Absolute change in sweat chloride concentration from baseline through week 24#

Absolute change in CFQ-R respiratory domain score from baseline through week 24#

Absolute change in BMI from baseline at week 24#

Absolute change in sweat chloride concentration from baseline at week 4

Absolute change in CFQ-R respiratory domain score from baseline at week 4

Other secondary end-points

Safety and tolerability based on AEs, clinical laboratory values, ECG findings, vital signs and pulse oximetry

Pharmacokinetics parameters of VX-659 or VX-445, TEZ, M1-TEZ and IVA

Time to first pulmonary exacerbation event through week 24#

Absolute change in BMI z-score from baseline at week 24#

Absolute change in body weight from baseline at week 24#

Open-label extension studies: VX17-659-105 and VX17-445-105

Primary end-point

Safety and tolerability based on AEs, clinical laboratory values, ECG findings, vital signs and pulse oximetry

Secondary end-points

Absolute change from baseline in FEV_1 % pred

Absolute change from baseline in sweat chloride concentration

Number of pulmonary exacerbation events

Time to first pulmonary exacerbation event

Absolute change from baseline in BMI

Absolute change from baseline in BMI z-score

Absolute change from baseline in body weight

Absolute change from baseline in CFQ-R respiratory domain score

MF: minimal function; FEV_1: forced expiratory volume in 1 s; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index; AE: adverse event; TEZ: tezacaftor; M1-TEZ: metabolite of tezacaftor; IVA: ivacaftor. #: patients with *F508del*/MF genotypes only (VX17-659-102 and VX17-445-102).

over 24 weeks and accounting for a 10% dropout rate, based on a two-sided, two-sample negative binomial regression model test for the ratio of rates at a significance level of 0.05, the power to detect a 40% reduction in pulmonary exacerbation rate for triple-combination groups compared with placebo groups in these studies is ~80%. To adjust for multiplicity, pulmonary exacerbations and other key secondary end-points will be tested only at the final analysis and only if the primary end-point shows statistical significance.

In studies in patients with the *F508del*/*F508del* genotype, assuming a within-group standard deviation 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 patients per treatment group is expected to have ~93% power to detect a difference of 5 percentage points in the mean absolute change in FEV_1 % pred from baseline at week 4.

In these studies, some additional end-points, such as absolute change in CFQ-R respiratory domain score, will be analysed using an MMRM model similar to that used for the primary end-point. The full analysis set will be used to assess efficacy and will include all randomised patients with the intended *CFTR* genotype who received one or more doses of study drug. The safety analysis will include all patients who received one or more doses of study drug.

Open-label extension studies: VX17-659-105 and VX17-445-105

Provided patients have not permanently discontinued the study drug in the parent study, patients who complete the randomised treatment periods for VX-659 or VX-445 in triple combination with TEZ/IVA

TABLE 5 Treatment periods and safety follow-up visits: open-label extension studies: VX17-659-105 and VX17-445-105

Event/assessment	Day 1	Day 15	Weeks 4, 8, 16, 24, 36	Week 48	Weeks 60, 72, 84	Week 96	ETT visit[#]	Safety follow-up[¶]
Clinic visit[+]	+	+	+	+	+	+	+	+
CFQ-R	+	–	Weeks 4, 8, 24	+	Week 72	+	+	+
Weight and height[§,f]	+	–	+	+	+	+	+	+
Spirometry	+	+	+	+	+	+	+	+
Sweat chloride concentration	+	+	Weeks 4, 8, 16, 24	–	–	+	–	–
Haematology/serum chemistry	+	+	+	+	+	+	+	+
Pharmacokinetics sampling	–	–	Week 4	–	–	–	–	–
Study drug count	+	+	+	+	+	+	+	–
AEs and SAEs[##]	+	+	+	+	+	+	+	+

ETT: early termination of treatment; CFQ-R: Cystic Fibrosis Questionnaire-Revised; AE: adverse event; SAE: serious AE. [#]: an ETT visit should be scheduled as soon as possible if a patient prematurely discontinues study treatment. [¶]: 28±7 days after the last dose of study drug (if applicable). [+]: additional telephone contact at weeks 12, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92. [§]: on day 15, weight and height measurements will be taken in study VX17-445-105, but not in study VX17-659-105. [f]: weight and height will be measured with shoes off. Height will be collected only for subjects ⩽21 years of age on the date of informed consent. For subjects >21 years of age, the height value obtained from the screening visit in the parent study will be used for the body mass index calculations. [##]: AEs and SAEs continuously assessed through completion of study participation.

(VX17-659-102 or VX17-659-103 and VX17-445-102 or VX17-445-103, respectively) will have the option to enrol in the respective open-label extension study VX17-659-105 (ClinicalTrials.gov identifier NCT03447262) or VX17-445-105 (ClinicalTrials.gov identifier NCT03525574) (table 1 and figure 3a and b). Each open-label extension study will include over 400 patients with eligible genotypes (*F508del*/MF or *F508del*/*F508del*). The primary end-point of the open-label extension studies is the safety and tolerability of long-term treatment with VX-659 or VX-445 in triple combination with TEZ/IVA. Evaluation of long-term efficacy is a secondary objective (table 4).

Each open-label extension study consists of a 96-week treatment period, during which patients receive the same dose of VX-659 or VX-445 triple combination used in the respective parent study, followed by a safety follow-up visit 4 weeks after the last dose of study drug. Safety will be evaluated in all patients who received one or more doses of study drug (table 5 and figure 3c).

Ethical approval and patient consent

All studies will be conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, consistent with the principles of the Declaration of Helsinki. Study documentation will be approved by institutional review boards/independent ethics committees before study initiation. Written informed consent (and assent, if applicable) will be obtained before participation.

Discussion

Here we describe remarkable progress from the pre-clinical stage to global phase 3 programmes evaluating two next-generation CFTR correctors, VX-659 and VX-445, in triple combination with the first-generation corrector TEZ and the potentiator IVA. Many factors contributed to the ability to design and conduct these unique programmes. First, understanding the multiple molecular deficits that result from the *F508del-CFTR* mutation led to the hypothesis that the response of the mutant protein to existing corrector–potentiator regimens could be further enhanced with the addition of a second corrector [25, 27]. Second, the strategy was based on a strong pre-clinical model that has been highly predictive of clinical results [9, 14]. Previous experience with *in vitro* HBE results translating into clinical improvement in FEV_1 % pred and other clinical outcomes provided confidence that triple combinations would be efficacious in patients with an *F508del*/MF or *F508del*/*F508del* genotype, a confidence that was reinforced by phase 2 results consistent with predicted estimates of clinical outcome [25, 27]. Third, prior experience with CFTR modulator clinical development programmes provided the basis for an efficient development strategy, including a 4-week primary efficacy end-point, that will potentially enable an expedited drug development programme in selected regions.

Cumulative experience with effective CFTR modulators allowed for the design of complementary studies in each of the triple-combination programmes, leveraging the 24-week placebo-controlled design in patients with *F508del*/MF genotypes to obtain safety data applicable to the *F508del*/MF and *F508del*/*F508del* populations and to provide long-term placebo-controlled data on the number of pulmonary

exacerbation events and other outcomes. Finally, these phase 3 programmes could not have been successfully conducted without the support of the Cystic Fibrosis Therapeutics Development Network in the USA and the European Cystic Fibrosis Clinical Trials Network, agreement and input from investigative teams, and willingness of patients to participate in the trials. Outreach, co-development and communication among the stakeholders enabled efficient trial design and conduct, while safety, consistency, and trial and data integrity were maintained. Together, these studies represent the culmination of a decade of pre-clinical and clinical experience with CFTR modulators to address the underlying protein defect caused by the *F508del-CFTR* mutation and to determine whether a triple-combination regimen can provide meaningful clinical benefits to the majority of patients with CF.

Conclusions

Extensive CFTR modulator experience was leveraged to design and conduct an unprecedented, efficient and data-driven phase 3 development programme investigating two triple-combination regimens in parallel in patients with one or two *F508del*-CFTR alleles. Data generated from this programme have the potential to demonstrate the substantial advancement in therapy that triple combinations provide over current therapies in both patient populations, by providing an effective CFTR modulator therapy for patients for whom no CFTR modulators are currently approved (*i.e. F508del*/MF genotypes) and an enhanced CFTR modulator therapy for patients with the *F508del*/*F508del* genotype. Approximately 90% of people with CF carry one or more copies of the *F508del-CFTR* allele, and this programme represents an important step towards potentially treating the underlying protein defect in these patients with a single highly effective triple-combination regimen.

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