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Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in People With Cystic Fibrosis and at Least One F508del Allele: 144-Week Interim Results From a 192-Week Open-label Extension Study

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**Summary**
This 144-week interim analysis of an open-label extension study in participants who completed the ELX/TEZ/IVA pivotal studies supports the favourable safety profile and durable, disease-modifying clinical benefits of ELX/TEZ/IVA.
Abstract

AIMS: In two pivotal Phase 3 trials, up to 24 weeks of treatment with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was efficacious and safe in patients with cystic fibrosis ≥12 years of age who have at least one F508del allele. The aim of this study is to assess long-term safety and efficacy of ELX/TEZ/IVA in these patients.

METHODS: In this Phase 3, open-label, single-arm extension study, participants with F508del-minimal function (from a 24-week parent study; n = 399) or F508del-F508del (from a 4-week parent study; n = 107) genotypes receive ELX/TEZ/IVA at the same dose (ELX 200 mg once daily, TEZ 100 mg once daily and IVA 150 mg every 12 hours). The primary endpoint is safety and tolerability. A prespecified interim analysis was conducted when the last participant reached the Week 144 visit.

RESULTS: At the Week 144 interim analysis, mean duration of exposure to ELX/TEZ/IVA in the extension study was 151.1 weeks. Exposure-adjusted rates of adverse events (586.6 events per 100 participant-years) and serious adverse events (22.4 events per 100 participant-years) were lower than in the ELX/TEZ/IVA treatment group in the 24-week parent study (1096.0 events per 100 participant-years and 36.9 events per 100 participant-years, respectively); most participants had adverse events classified as mild (16.4% of participants) or moderate (60.3% of participants) in severity. Fourteen participants (2.8%) had adverse events that led to treatment discontinuation. Following initiation of ELX/TEZ/IVA, participants had increases in per cent predicted FEV₁ (ppFEV₁), Cystic Fibrosis Questionnaire-Revised respiratory domain score and body mass index, and had decreases in sweat chloride concentration and pulmonary exacerbations rates that were maintained over
the interim analysis period. The mean annualised rate of change in ppFEV₁ was +0.07 percentage points (95% CI, −0.12 to 0.26) among the participants.

CONCLUSIONS: ELX/TEZ/IVA was generally safe and well-tolerated, with a safety profile consistent with the 24-week parent study. Participants had sustained improvements in lung function, respiratory symptoms, CFTR function, pulmonary exacerbation rates and nutritional status. These results support the favourable safety profile and durable, disease-modifying clinical benefits of ELX/TEZ/IVA.

Abstract word count: 333 (limit: 250)

Key words: cystic fibrosis, elexacaftor, tezacaftor, ivacaftor, long-term
Introduction

Cystic fibrosis (CF), a life-shortening autosomal recessive disease that affects more than 100,000 adults and children worldwide (1-4), is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, which decrease the quantity and/or function of the CFTR protein, an anion channel present at the surface of a variety of epithelial cells, leading to impaired transport of chloride and bicarbonate (2, 3, 5). These molecular defects manifest clinically in respiratory, pancreatic, hepatic and gastrointestinal dysfunction (6).

Ivacaftor (IVA) is a CFTR potentiator that augments the impaired CFTR gating associated with some CFTR mutations (7). Treatment with IVA led to improvements in per cent predicted forced expiratory volume in 1 second (ppFEV₁), Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score and sweat chloride concentration, along with increases in weight and reductions in the rate of pulmonary exacerbations, in patients with at least one CFTR gating mutation (8-10). An open-label extension study of IVA showed that improvements in lung function, weight, and pulmonary exacerbations were maintained for up to 144 weeks, and another study reported an annual rate of lung function decline nearly 50% lower in patients receiving IVA than in those receiving only symptomatic treatment (10, 11). These results established that a CFTR modulator can provide effective, long-term, disease-modifying treatment for CF.

Elexacaftor (ELX) and tezacaftor (TEZ) are CFTR correctors that act via complementary mechanisms to ameliorate the CFTR protein processing and trafficking defects intrinsic to the F508del mutation (12). F508del is the most common CFTR mutation; up to 90% of people with CF have at least one F508del allele (13). The combination of TEZ and IVA improved lung function and decreased sweat chloride concentration in patients homozygous for
*F508del (F/F)* (14, 15). TEZ/IVA resulted in improvements that were generally maintained for up to 96 weeks in an open-label extension study; patients had an annual rate of lung function decline that was 61.5% slower than that seen among patients who were not taking CFTR modulators (16).

The efficacy and safety of the triple combination of ELX, TEZ and IVA (ELX/TEZ/IVA) were established in two Phase 3 pivotal trials in people with CF ≥12 years of age who were heterozygous for *F508del* and a minimal function mutation (*F/MF*) or had the *F/F* genotype (17-19). In both trials, ELX/TEZ/IVA treatment led to significant improvements in ppFEV₁, CFQ-R respiratory domain score and sweat chloride concentration. In patients with the *F/F* genotype, these improvements were superior to those seen with TEZ/IVA. To assess the long-term safety and efficacy of extended ELX/TEZ/IVA use, a 192-week open-label extension study was initiated in participants who completed one of these pivotal studies. Here, we report results from the Week 144 interim analysis of this extension study.
Methods

Participants, Trial Design and Oversight

Study VX17-445-105 (Study 445-105, NCT03525574) is a Phase 3, multicentre, open-label extension study that enrolled participants ≥12 years of age with CF and either F/MF (from Study VX17-445-102 [Study 445-102, NCT03525444]) or F/F (from Study VX17-445-103 [Study 445-103, NCT03525548]) genotypes. To enrol in this extension study, participants must have completed study drug treatment or completed study visits up to the last scheduled visit of the treatment period in parent studies 445-102 or 445-103. For a complete list of inclusion and exclusion criteria and additional details on study design, dosing and statistical analysis, see the online supplement.

The extension study is designed to evaluate long-term safety and efficacy of ELX/TEZ/IVA over a 192-week treatment period (Figure S1). All participants regardless of parent study assignment receive ELX/TEZ/IVA at the same dose level that was evaluated in the parent studies (ELX 200 mg once daily, TEZ 100 mg once daily and IVA 150 mg every 12 hours). An interim analysis with prespecified analyses was conducted after the last patient completed the Week 144 visit.

The trial was designed by Vertex Pharmaceuticals Incorporated in collaboration with the authors. Informed consent was provided by all participants or their parent or legal guardian; assent was obtained from patients in accordance with local requirements. Safety was monitored by an independent data safety monitoring committee, and data collection and analysis were performed by Vertex Pharmaceuticals in collaboration with the authors and the VX17-445-105 Study Group. All authors had full access to the trial data, critically reviewed the manuscript and approved it for submission. Investigators vouch for the accuracy and
completeness of the data generated at their respective sites, and the investigators and Vertex Pharmaceuticals vouch for the fidelity of the trial to the protocol.

Due to this study overlapping with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a global protocol addendum was implemented. Participant access to study drug therapy and collection of safety data were prioritised. Measures were implemented in accordance with country and local regulations, as well as site-level considerations, and included, as applicable, remote consent, shipment of study drug to the participant’s home, virtual study visits conducted by site personnel via teleconference, home nursing visits for blood draws, in-home assessments and remote monitoring.

The clinical trial protocol, SARS-CoV-2–related protocol addendum and informed consent forms were approved by independent ethics committees for each region or site, as required by local regulations.

**Outcome Measures**

The primary endpoint of the study is safety and tolerability as assessed by adverse events, clinical laboratory values, electrocardiograms, vital signs and pulse oximetry. Secondary endpoints include absolute changes in ppFEV₁, sweat chloride concentration, CFQ-R respiratory domain score (range, 0 to 100; higher scores indicate higher patient-reported quality of life with regards to respiratory symptoms) and body mass index (BMI) from parent study baseline, as well as number of pulmonary exacerbations. The rate of lung function change was determined by calculating the annualised rate of change of ppFEV₁ in a post hoc analysis.
Statistical Analysis

Analyses of safety and efficacy included all participants who received at least one dose of ELX/TEZ/IVA in the extension study. For all efficacy endpoints, data for participants with F/MF genotypes (parent Study 445-102) were analysed separately from those for participants with the F/F genotype (parent Study 445-103). The main analyses were based on data collected up to the date the last participant reached the Week 144 visit (i.e., the data lock date). The main analyses of safety were based on all events collected up to the data lock date and included both in-clinic and at-home assessments. The main analyses for the efficacy endpoints included data collected up to Week 144 and all subsequent scheduled or unscheduled visits (Extended Week 144).

The Extended Week 144 Visit is an extension to include the Week 144 Visit and all subsequent scheduled or unscheduled visits. For participants who have Week 144 Visit assessments, the Week 144 assessment was used. For participants whose Week 144 Visit assessment was missing, the most recent visit assessment beyond Week 144, if available, was used.

Analysis of ppFEV\textsubscript{1}, sweat chloride concentration and BMI used only in-clinic data while CFQ-R respiratory domain score used both in-clinic and at-home assessments.

Absolute change from baseline in ppFEV\textsubscript{1}, sweat chloride concentration, CFQ-R respiratory domain score and BMI were analysed using a mixed-effects model for repeated measures. For participants transitioning from Study 445-102, the model included treatment group (as randomised in the parent study), visit and treatment by visit interaction as fixed effects with continuous baseline ppFEV\textsubscript{1} from the parent study, age at screening for the parent study (<18 years versus ≥18 years) and sex (male versus female) as covariates. For participants transitioning from Study 445-103, the analysis was similar with the exception that sex was
not a covariate in the model. Number of pulmonary exacerbations was analysed using a negative binomial regression model which was the same as in the respective parent study.

We conducted a post hoc analysis for the annualised rate of change of ppFEV$_1$ in participants with $F/MF$ and the $F/F$ genotypes, as well as a pooled analysis that included all participants. The annualised rate of change in ppFEV$_1$ was estimated using a linear mixed-effects model, excluding measures during the first 21 days of ELX/TEZ/IVA treatment to avoid inclusion of acute lung function improvement.

**Results**

**Population**

The trial was conducted at 110 sites in North America, Australia and Europe. Overall, 506 participants ($n = 399$ with $F/MF$ genotypes and $n = 107$ with $F/F$ genotype) entered the open-label extension and received $\geq 1$ dose of ELX/TEZ/IVA, representing 99.2% of participants in the parent studies. Additional detail on participant disposition is provided in **Figure 1**.

Participant demographics and clinical characteristics at baseline are provided in **Table 1** and **Supplementary Table S1**. The mean exposure to ELX/TEZ/IVA during the interim analysis period of this trial was 151.1 weeks (standard deviation [SD], 33.7). A total of 433 participants were still receiving treatment with ELX/TEZ/IVA in this extension study at Week 144; 73 participants discontinued, with the majority either changing to commercial ELX/TEZ/IVA ($n = 24$), refusing further dosing ($n = 18$), or having AEs that led to treatment discontinuation ($n = 10$) (see Figure 1 for all participant dispositions).

**Safety**

ELX/TEZ/IVA treatment was generally safe and well-tolerated. During this 144-week interim analysis period, 98.8% of participants had at least one adverse event (AE). Most
participants had AEs that were classified as mild (16.4%) or moderate (60.3%) in severity (Table 2). The most common AEs reported in participants were infective pulmonary exacerbation (44.5%), cough (41.9%), headache (32.8%), oropharyngeal pain (28.9%) and nasopharyngitis (26.7%). Serious AEs were reported in 154 participants (30.4%). Fourteen participants (2.8%) discontinued treatment. This included 10 participants with discontinuations attributed to AEs, two participants with discontinuations attributed to physician decision due to AEs, one participant who died during the study due to an AE of accidental oxycodone toxicity that was considered by the investigator to be unrelated to study drug, and one participant who had an AE prior to the start of this extension study and was not dosed in the extension study. The AEs leading to treatment discontinuation in the remaining participants were elevated transaminases (n = 6), hepatic encephalopathy in a participant with a medical history of cirrhosis and portal hypertension (n = 1), rash (n = 1), depression (n = 1), myalgia (n = 1) and anorexia nervosa (n = 1), as well as a participant with tinnitus, sinus discomfort and dizziness (n = 1), all of which resolved, and recurrence of postural orthostatic tachycardia syndrome (n = 1) in one participant with a prior medical history, which was not considered related to study drug and had not resolved as of the data cut-off date for this analysis.

The exposure-adjusted rates of AEs and serious AEs in the extension study were lower than those seen in participants with F/MF genotypes in the active arm of the 24-week parent study that forms the basis of the ELX/TEZ/IVA safety profile (Table 2; Supplementary Table S2; Supplementary Table S3). The overall exposure-adjusted rate of AEs in the 144-week interim analysis was 586.6 events per 100 participant-years compared with 1288.0 events per 100 participant-years for participants in the placebo arm of the parent study.

Consistent with previous clinical trials of ELX/TEZ/IVA (17, 18), data related to aminotransferases, rash, creatine kinase and blood pressure were reviewed. Elevated levels of
alanine aminotransferase and/or aspartate aminotransferase greater than three, five and eight times the upper limit of normal were reported in 57 (11.3%), 32 (6.3%) and 11 (2.2%) participants, respectively (Supplementary Table S4). Two participants (0.4%) had levels of alanine aminotransferase and/or aspartate aminotransferase greater than three times the upper limit of normal concurrent with bilirubin greater than two times the upper limit of normal: one participant had Gilbert’s syndrome and elevated total bilirubin (mostly indirect) throughout the study, and the other participant had concurrent elevations that resolved with study drug discontinuation. Eighty-two participants (16.2%) had AEs of elevated transaminases; in 6 participants (1.2%) the AE was considered serious. Twenty-one participants (4.2%) interrupted treatment due to AEs of elevated transaminases, and 6 participants (1.2%) discontinued. Eighty-two participants (16.2%) had rash events, of whom 33 were male and 49 were female. Two participants (0.4%) had rash events that were considered serious (Supplementary Table S5). One participant discontinued due to an AE of rash. Sixty-five participants (12.8%) had AEs of blood creatine phosphokinase increased, one of whom had a serious AE that resolved without change in study drug dosing (Supplementary Table S6). Three participants (0.6%) had AEs of rhabdomyolysis that presented with blood creatine kinase elevations; none had symptoms consistent with rhabdomyolysis syndrome, and before onset, all 3 participants had exercised. One participant (0.2%) discontinued due to an AEs of blood creatine phosphokinase increased and alanine aminotransferase increased. The exposure-adjusted rates of AEs of transaminase elevations, rash and creatine kinase elevations were lower than those in the 24-week parent study. Mean (SD) systolic and diastolic blood pressures increased by 3.9 (12.5) mm Hg and 2.6 (9.0) mm Hg, respectively, from initiation of ELX/TEZ/IVA treatment (Supplementary Table S7). Sixteen participants (3.2%) had AEs related to elevated blood pressure. One participant with type 2 diabetes, chronic kidney disease and a history of hypertension had a serious AE of
hypertensive urgency which was not considered related to study drug and did not require change in ELX/TEZ/IVA dosing. All other AEs of elevated blood pressure were non-serious and did not require change in ELX/TEZ/IVA dosing; seven of the 16 participants required medication for elevated blood pressure (Supplementary Table S8). Other clinical or laboratory assessments did not reveal any notable safety findings.

**Efficacy**

*F508del-minimal function genotypes*

At Extended Week 144, there was a mean absolute increase in ppFEV₁ from parent study baseline of 14.8 percentage points (95% CI, 13.3 to 16.3) for participants who previously received placebo in the parent study (n = 161) and 14.1 percentage points (95% CI, 12.6 to 15.6) for participants who previously received ELX/TEZ/IVA (n = 166) (Table 3, Figure 2a). The annualised rate of pulmonary exacerbations was 0.20 (95% CI, 0.16 to 0.24) (Table 3). At Extended Week 144, the mean absolute change in sweat chloride concentration from parent study baseline was −50.5 mmol/L (95% CI, −53.4 to −47.7) for participants who previously received placebo in the parent study (n = 146) and −47.2 mmol/L (95% CI, −49.9 to −44.4) for participants who previously received ELX/TEZ/IVA (n = 160) (Table 3, Figure 2b). The mean absolute change in CFQ-R respiratory domain score from parent study baseline was 17.6 points (95% CI, 14.9 to 20.2) for participants who previously received placebo in the parent study (n = 175) and 19.1 points (95% CI, 16.4 to 21.8) for participants who previously received ELX/TEZ/IVA (n = 171) (Table 3, Figure 2c). The mean absolute change in BMI was 1.76 kg/m² (95% CI, 1.48 to 2.05) from parent study baseline for participants who previously received placebo in the parent study (n = 167) and 1.61 kg/m² (95% CI, 1.32 to 1.90) for participants who previously received ELX/TEZ/IVA (n = 169) (Table 3, Figure 2d).
**F508del-F508del genotype**

At Extended Week 144, the mean absolute change in ppFEV₁ from parent study baseline was 12.0 percentage points (95% CI, 9.5 to 14.5) for participants who previously received TEZ/IVA in the parent study (n = 44) and 11.6 percentage points (95% CI, 9.1 to 14.0) for participants who previously received ELX/TEZ/IVA (n = 48) (Table 4, Figure 3a). The annualised rate of pulmonary exacerbations was 0.18 (95% CI, 0.12 to 0.26) (Table 4). At Extended Week 144, the mean absolute change in sweat chloride concentration from parent study baseline was −53.4 mmol/L (95% CI, −57.7 to −49.0) for participants who previously received TEZ/IVA in the parent study (n = 42) and −49.9 mmol/L (95% CI, −54.1 to −45.7) for participants who previously received ELX/TEZ/IVA (n = 47) (Table 4, Figure 3b). The mean absolute change in CFQ-R respiratory domain score from parent study baseline was 13.9 points (95% CI, 9.2 to 18.6) for participants who previously received TEZ/IVA in the parent study (n = 45) and 18.2 points (95% CI, 13.6 to 22.7) for participants who previously received ELX/TEZ/IVA (n = 48) (Table 4, Figure 3c). The mean absolute change in BMI was 1.50 kg/m² (95% CI, 1.11 to 1.89) from parent study baseline in participants who previously received TEZ/IVA in the parent study (n = 44) and 1.74 kg/m² (95% CI, 1.36 to 2.12) in participants who previously received ELX/TEZ/IVA (n = 48) (Table 4, Figure 3d).

**Annualised rate of change in ppFEV₁**

In an analysis assessing lung function change over time, the annualised rate of change in ppFEV₁ was +0.08 percentage points (95% CI, −0.14 to 0.30) for participants with F/MF genotypes and +0.03 percentage points (95% CI, −0.33 to 0.39) for participants with the F/F genotype (Supplementary Table S9). As the rate of change was similar for both genotype groups, a pooled analysis of the annualised rate of change in ppFEV₁ that included all
participants was conducted. In this pooled analysis, the annualised rate of change in ppFEV\(_1\) was +0.07 percentage points (95% CI, −0.12 to 0.26) (Supplementary Table S9).

**Discussion**

In this extension study of ELX/TEZ/IVA in participants ≥12 years of age with at least one \(F508\)del allele, ELX/TEZ/IVA treatment was generally safe and well-tolerated and led to sustained and clinically meaningful improvements in lung function, respiratory symptoms, CFTR function and nutritional status. Participants also had lower rates of pulmonary exacerbations than seen with previous CFTR modulator regimens. Because people with CF are likely to require long-term treatment with ELX/TEZ/IVA or similar CFTR modulator regimens, safety and efficacy data spanning several years, as demonstrated in this study, are crucial for making informed patient care decisions.

At the time of this interim analysis, 433 participants of the 506 originally enrolled remained in the study; 73 participants discontinued, with the majority either changing to commercial ELX/TEZ/IVA (n = 24), refusing further dosing (n = 18), or having AEs that led to treatment discontinuation (n = 10). Overall, participants had a mean exposure to ELX/TEZ/IVA of 151.1 weeks. For most participants, AEs were mild or moderate in severity and generally consistent with common manifestations of CF. The overall exposure-adjusted rates of AEs and serious AEs were lower than those in the 24-week parent study. Data related to transaminase elevations, rash events, creatine kinase elevations and blood pressure, as well as AEs leading to treatment discontinuation, were generally consistent with the established safety profile based on the 24-week parent study. Rash events were mainly non-serious, manageable and occurred more frequently in female participants than male participants. Consistent with the 24-week parent study, participants had small increases in both systolic and diastolic blood pressure. In the current extension study, one participant with a medical
history of depression had a nonserious AE of depression that resolved after treatment discontinuation. Overall, the incidences of AEs of depression and anxiety were 7.1% and 6.3%, respectively, during this 144-week treatment period, equal to 2.69 and 2.63 events per 100 participant years, respectively, and were generally consistent with the rates seen in previous interim analyses as well as in the pivotal 24-week parent study. In an integrated analysis of clinical trials of CFTR modulators, the exposure-adjusted rate of depression-related AEs was 3.32 events per 100 participant years in the pooled ELX/TEZ/IVA group (N=1711; 3857 participant years of exposure) and 3.24 events per 100 participant years in the pooled placebo group (N=1369; 709 participant years of exposure) (Supplementary Table S10). It is important to note that previous studies found symptoms of depression were elevated in people with CF, with Quittner et al reporting that among 6088 patients with CF, 5% to 19% of adolescents and 13% to 29% of adults had elevated symptoms of depression (20). Our results suggest that participants taking ELX/TEZ/IVA in these clinical trials have rates of depression-related adverse events consistent with background. The overall safety results demonstrate a favourable long-term safety profile for ELX/TEZ/IVA.

In the pivotal 445-102 and 445-103 trials, participants who received ELX/TEZ/IVA had rapid and statistically significant increases in ppFEV\textsubscript{1} and CFQ-R respiratory domain score along with significant decreases in sweat chloride concentrations (17, 18). For participants who received the control regimen in these parent studies, ELX/TEZ/IVA treatment in the extension study led to increases in ppFEV\textsubscript{1} and CFQ-R respiratory domain scores and decreases in sweat chloride concentration that were consistent with those seen in participants who received ELX/TEZ/IVA in the parent studies. Crucially, all these improvements in efficacy outcome measures were sustained through the end of the 144-week interim analysis period, establishing the durability of treatment response and disease-modifying benefits with ELX/TEZ/IVA.
Given the robust and durable improvements in ppFEV$_1$ seen in this interim analysis, we sought to further quantify the impact of ELX/TEZ/IVA treatment on CF lung disease progression by conducting an analysis of the rate of change in lung function over time. Previous studies with IVA and TEZ/IVA showed that lung function declines more slowly in people with CF treated with IVA or TEZ/IVA than in those not taking CFTR modulators (by nearly 50% and 61.5%, respectively), indicating that these therapies can modify CF disease progression by slowing lung function decline (11, 16). In contrast, through Week 144 of this extension study, the pooled participant population had a mean annual increase in ppFEV$_1$ of 0.07 percentage points (95% CI, −0.12 to 0.26), indicating that across a CF population with at least one $F508del$ allele, there was no mean loss of pulmonary function over 144 weeks of ELX/TEZ/IVA treatment. These results raise for the first time the potential that a CFTR modulator therapy could halt loss of lung function in patients with CF over an extended period of time.

Participants taking ELX/TEZ/IVA in the parent studies had steady and sustained increases in BMI (17, 18). While the mean BMI for each genotype group was within the normal range at the respective parent study baselines, it is important to understand long-term impacts of ELX/TEZ/IVA on nutritional status (21). Overall, the mean BMI increased rapidly during the first 24 weeks of treatment with ELX/TEZ/IVA with smaller increases and slight variations during the remainder of the interim analysis period. Importantly, at Week 144 mean BMI remained in the normal range. This result suggests ELX/TEZ/IVA generally leads to rapid improvement in nutritional status which is then maintained over time.

Reducing the number of pulmonary exacerbations is critical to averting the progressive lung function decline seen in patients with CF (22). During the first 144 weeks of this extension study, the estimated pulmonary exacerbation rate for patients with $F/MF$ genotypes (0.20) was lower than in the ELX/TEZ/IVA arm of the 24-week parent study (0.37) (18), and the
rate of pulmonary exacerbations for participants in both genotype groups was lower than in the previous 24-week interim analysis of this extension study (0.19 versus 0.30) (23). Because this study overlapped with the SARS-CoV-2 pandemic, restrictions on social interactions might have also reduced the incidence of pulmonary exacerbation among the study participants (24). Nonetheless, it is clear that the reduction in pulmonary exacerbations observed in the parent study was maintained in this 144-week extension, supporting the durable benefits of ELX/TEZ/IVA.

One limitation of the current extension study is lack of direct comparator group which limits the interpretation of safety and efficacy data. For this reason, safety and efficacy results were compared to the placebo treatment group in the 445-102 parent study. Additionally, it should be noted the participants in this extension study had to meet specific inclusion criteria for enrolment into the pivotal trials and therefore extrapolation of these results to all people with CF will likely require studies of real-world usage of ELX/TEZ/IVA. However, results from studies on the safety and efficacy of real-world use of ELX/TEZ/IVA have been consistent with the results reported here (25).

In conclusion, ELX/TEZ/IVA was generally safe and well-tolerated through Week 144 of this extension study, with a safety profile consistent with the pivotal 24-week parent study. The clinically meaningful improvements in measures of lung function, respiratory symptoms, CFTR function, pulmonary exacerbation rates and nutritional status reported for patients treated with ELX/TEZ/IVA in the two pivotal Phase 3 studies were maintained through this longer-term analysis period. These results, along with the finding of no mean loss in pulmonary function over 144 weeks of treatment, further support the durable and disease-modifying benefits of ELX/TEZ/IVA.
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Conflicts of Interest

All authors received nonfinancial support (assistance with manuscript preparation) from Nucleus Global, which received funding from Vertex Pharmaceuticals Incorporated. Additional disclosures are as follows: CLD has nothing further to disclose. ET has received consulting, speaker and travel fees from Vertex Pharmaceuticals. SC serves on advisory board for Vertex Pharmaceuticals. RWL serves on advisory board and reports grants paid to her institution and consulting fees from Vertex Pharmaceuticals. MAM reports patient recruitment fees paid to his institution and advisory fees from Vertex Pharmaceuticals; consulting fees from Antabio, Arrowhead Pharmaceuticals, Boehringer Ingelheim, Enterprise Therapeutics, Santhera, Sterna Biologicals and Vertex Pharmaceuticals; and speaker fees from Arrowhead Pharmaceuticals, Boehringer Ingelheim and Vertex Pharmaceuticals; travel fees from Boehringer Ingelheim and Vertex Pharmaceuticals; advisory fees from Antabio, Arrowhead Pharmaceuticals, Boehringer Ingelheim, Enterprise Therapeutics, Kither Biotech, Santhera and Vertex Pharmaceuticals; and serves on the European Cystic Fibrosis Society (ECFS) Board. EFM reports grants, lecture fees and serving on an advisory board for Vertex
Pharmaceuticals; lecture fees from Roche; travel fees from A. Menarini; and serving on advisory boards for Janssen, Insmed and CF Storm. DP reports grants from Laurent Pharmaceuticals, Parion Sciences, Proteostasis Therapeutics and Vertex Pharmaceuticals; consulting fees from Vertex Pharmaceuticals; non-financial support for travel to investigator meeting from Vertex Pharmaceuticals; and serves on advisory board for Sanofi. BSQ reports payments paid to his institution and speaker fees from Vertex Pharmaceuticals. FCR reports grants paid to his institution from Basilea Pharmaceutica, German Center for Lung Research (DZL), German Center for Infection Research (DZIF), Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis (iABC)/Innovative Medicines Initiative (IMI), European Federation of Pharmaceutical Industries and Associations (EFPIA), Insmed, Novartis and Polyphor; consulting fees from Grifols, Insmed, Parion, Shionogi and Zambon; speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Grifols, Insmed and Novartis; serves on advisory board for Grifols, Insmed, Parion, Shionogi and Zambon; unpaid honoraria as co-chair of the German Bronchiectasis Registry (PROGNOSIS), a steering committee member of the European Bronchiectasis Registry (EMBARC), a steering committee member of the European NTM registry (EMBARC-NTM), a core network lead in ERN-LUNG, a principal investigator for DZL, a chair of the cystic fibrosis working group of the German Respiratory Society (DGP), a steering committee member of the Group of German CF Physicians (AGAM), and co-chair of medical consultants of PCD Patient Advocacy Group (Kartagener Syndrom und Primäre Ciliäre Dyskinesie e.V.); and payments to his institution from AbbVie, AstraZeneca, Boehringer Ingelheim, Corbus, Celtaxsys, Insmed, Novartis, Parion, Polyphor, Vertex and Zambon. SMR reports grants paid to his institution from AbbVie, Arrowhead Pharmaceuticals, AstraZeneca, Bayer, Celtaxsys, Eloxx, Ionis Pharmaceuticals, Novartis, Proteostasis Therapeutics, Synedgen, Synspira Therapeutics, Translate Bio and Vertex Pharmaceuticals; non-financial support from AbbVie, Ionis Pharmaceuticals, Proteostasis
Therapeutics, Renovion, Synedgen and Synspira Therapeutics; consulting fees from AbbVie, Arrowhead Pharmaceuticals, Bayer, Cystetic Medicines, Ionis Pharmaceuticals, Novartis, Renovion, Synedgen, Synspira Therapeutics and Vertex Pharmaceuticals; and serves as Co-chair for the Next Generation Steering Committee on Vertex Pharmaceuticals. HS has nothing further to disclose. JLT-C serves on the board of trustees, clinical research executive committee, clinical research advisory board and Women’s Health Research-Working Group for the US Cystic Fibrosis Foundation; serves on the scientific advisory board for Emily’s Entourage; serves on the respiratory health awards working group, scientific grants review committee and clinical problems assembly programming committee for the American Thoracic Society; consulting fees from 4D Molecular Therapeutics, Celtaxsys, Prolarean Imaging, Protalix Biotherapeutics, Proteostasis Therapeutics and Santhera Pharmaceuticals; grants to her institution from Bayer, Celtaxsys, Eloxx Pharmaceuticals, Gilead, N30 and Proteostasis Therapeutics; speaking fees from Celtaxsys and Gilead; serves on advisory board for AbbVie, Genentech, Insmed and Novartis; and is an associate editor for the Journal of Cystic Fibrosis. NJW reports lecture fees from Vertex Pharmaceuticals and serves on advisory board for Vertex Pharmaceuticals and Proteostasis Therapeutics. BR reports travel fees, grants from, and serves on advisory board for Vertex Pharmaceuticals; and personal fees from Cystetic Medicines. MG reports grants to his institution from Vertex Pharmaceuticals. NA, SMM, VP-C, YVT, ST, TW, FX and YZ are employees of Vertex and may own stock or stock options in Vertex.

Author contributions

The study sponsor (Vertex Pharmaceuticals Incorporated) designed the protocol in collaboration with the academic authors. Site investigators collected the data, which were analysed by the sponsor. All authors had full access to the study data. C.L.D., E.T., S.M.M.,
V. P-C., T.W., B.R. and M.G. developed the initial draft of the manuscript, with writing assistance from the sponsor. All authors participated in subsequent revisions. All authors approved the final version submitted for publication.

Sources of support

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References


Table 1. Demographics and Clinical Characteristics of Participants at Baseline*

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<th>Sub-group of Participants from Parent Study 445-103</th>
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<td>F/MF Genotypes</td>
<td>F/F Genotypes</td>
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<td>Placebo N = 203</td>
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<td>ELX/TEZ/IVA N = 506</td>
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<tr>
<td>Sex, n (%)</td>
<td>98 (48.3)</td>
<td>28 (53.8)</td>
<td>251 (49.6)</td>
</tr>
<tr>
<td></td>
<td>94 (48.0)</td>
<td>31 (56.4)</td>
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<td>Age, mean (SD), years</td>
<td>26.8 (11.3)</td>
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<td>26.7 (10.7)</td>
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<td>60 (29.6)</td>
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<td>≥12 to &lt;18 years</td>
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<td>≥18 years</td>
<td>143 (70.4)</td>
<td>38 (73.1)</td>
<td>361 (71.3)</td>
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<td></td>
<td>141 (71.9)</td>
<td>39 (70.9)</td>
<td></td>
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<td>Ethnicity, n (%)</td>
<td>12 (5.9)</td>
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<td>Hispanic or Latino</td>
<td>4 (2.0)</td>
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<tr>
<td>Not Hispanic or Latino</td>
<td>175 (86.2)</td>
<td>49 (94.2)</td>
<td>460 (90.9)</td>
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<td></td>
<td>184 (93.9)</td>
<td>52 (94.5)</td>
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<td>Sub-group of Participants from Parent Study 445-103</td>
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<td>$F$/MF Genotypes</td>
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<td>N = 203</td>
<td>N = 52</td>
<td>N = 506</td>
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<tr>
<td>Not collected per local regulations</td>
<td>16 (7.9)</td>
<td>0</td>
<td>25 (4.9)</td>
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<td><strong>Race, n (%)†</strong></td>
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<td></td>
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<tr>
<td>White</td>
<td>184 (90.6)</td>
<td>52 (100.0)</td>
<td>473 (93.5)</td>
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<td>Black or African American</td>
<td>2 (1.0)</td>
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<td>6 (1.2)</td>
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<td>Asian</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
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<td>American Indian or Alaska Native</td>
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<td>0 (0)</td>
<td>1 (0.2)</td>
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<tr>
<td>Other</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>3 (0.6)</td>
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<tr>
<td>Not collected per local regulations</td>
<td>16 (7.9)</td>
<td>0 (0)</td>
<td>25 (4.9)</td>
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<tr>
<td><strong>Geographical region, n (%)</strong></td>
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<tr>
<td>North America</td>
<td>120 (59.1)</td>
<td>33 (63.5)</td>
<td>304 (60.1)</td>
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<td>Sub-group of Participants from Parent Study 445-102</td>
<td>Sub-group of Participants from Parent Study 445-103</td>
<td>All Participants in Study 445-105</td>
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<td>$F/MF$ Genotypes</td>
<td>$F/F$ Genotypes</td>
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<td>TEZ/IVA</td>
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<tr>
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<td>N = 203</td>
<td>N = 196</td>
<td>N = 52</td>
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<td>Europe and Australia</td>
<td>83 (40.9)</td>
<td>79 (40.3)</td>
<td>19 (36.5)</td>
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<td>ppFEV₁, mean (SD), percentage points</td>
<td>61.3 (15.5)</td>
<td>61.4 (14.9)</td>
<td>60.2 (14.4)</td>
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<td>ppFEV₁ category, n (%)‡</td>
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<tr>
<td>&lt;40</td>
<td>16 (7.9)</td>
<td>18 (9.2)</td>
<td>4 (7.7)</td>
</tr>
<tr>
<td>≥40 to &lt;70</td>
<td>120 (59.1)</td>
<td>112 (57.1)</td>
<td>34 (65.4)</td>
</tr>
<tr>
<td>≥70 to ≤90</td>
<td>62 (30.5)</td>
<td>65 (33.2)</td>
<td>14 (26.9)</td>
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<tr>
<td>&gt;90</td>
<td>5 (2.5)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
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<td>Sweat chloride concentration, mean (SD), mmol/L</td>
<td>102.9 (9.8)</td>
<td>102.4 (11.9)</td>
<td>90.0 (12.3)</td>
</tr>
<tr>
<td>CFQ-R respiratory domain score, mean (SD), points</td>
<td>70.0 (17.8)</td>
<td>68.2 (16.8)</td>
<td>72.6 (17.9)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>21.31 (3.14)</td>
<td>21.53 (3.08)</td>
<td>21.88 (4.12)</td>
</tr>
</tbody>
</table>
Definition of abbreviations: BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; ppFEV₁ = per cent predicted forced expiratory volume in 1 second; SD = standard deviation; TEZ/IVA = tezacaftor/ivacaftor.

* Demographics and baseline characteristics of the full analysis set, which was defined as all enrolled participants who received ≥1 dose of study drug in the open-label extension study (Study 445-105). Baseline characteristics are based on data obtained at parent study baseline, which was defined as the most recent non-missing measurement before the first dose of study drug in the parent study treatment period (Study 445-102 or Study 445-103). Baseline in Study 445-103 was assessed after a 4-week run-in period with TEZ/IVA.

† The race categories may sum to >100% due to participants being able to indicate more than one race.

‡ Although those eligible for enrolment were required to have ppFEV₁ ≥40 at screening, there were some participants who had decreases to <40 by baseline.

§ The baseline mean sweat chloride value is a composite from participants with F/MF and F/F genotypes with different baseline values and is weighted towards the F/MF baseline due to the larger number of participants in this genotype subgroup (n = 399 F/MF; n = 107 F/F).
Table 2. Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Parent Study 445-102†</th>
<th>ELX/TEZ/IVA N = 202</th>
<th>ELX/TEZ/IVA N = 506</th>
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<tr>
<td></td>
<td>Mean Exposure = 23.7 Weeks</td>
<td>Mean Exposure = 23.6 Weeks</td>
<td>Mean Exposure = 151.1 Weeks</td>
</tr>
<tr>
<td>Participants</td>
<td>Events/100PY</td>
<td>Participants</td>
<td>Events/100PY</td>
</tr>
<tr>
<td>Any adverse event, n (%)</td>
<td>193 (96.0)</td>
<td>188 (93.1)</td>
<td>1096.01</td>
</tr>
<tr>
<td>Adverse events by maximum severity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>53 (26.4)</td>
<td>N/A</td>
<td>67 (33.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>125 (62.2)</td>
<td>N/A</td>
<td>102 (50.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (7.0)</td>
<td>N/A</td>
<td>19 (9.4)</td>
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<tr>
<td>Life threatening</td>
<td>1 (0.5)</td>
<td>N/A</td>
<td>0 (0)</td>
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<td>Serious adverse events, n (%)</td>
<td>42 (20.9)</td>
<td>67.05</td>
<td>28 (13.9)</td>
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<tr>
<td>Adverse events leading to treatment discontinuation, n (%)</td>
<td>0 (0)</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Adverse events leading to death, n (%)</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Parent Study 445-102†</td>
<td>Study 445-105 Week 144 Interim Analysis</td>
<td></td>
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<td>-----------------------</td>
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<td></td>
<td>Placebo N = 201</td>
<td>ELX/TEZ/IVA N = 202</td>
<td>ELX/TEZ/IVA N = 506</td>
</tr>
<tr>
<td>Mean Exposure = 23.7 Weeks</td>
<td>Mean Exposure = 23.6 Weeks</td>
<td>Mean Exposure = 151.1 Weeks</td>
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</tr>
<tr>
<td>Participants Events/100PY</td>
<td>Participants Events/100PY</td>
<td>Participants Events/100PY</td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to treatment interruption, n (%)</td>
<td>10 (5.0) 14.01</td>
<td>19 (9.4) 25.95</td>
<td>49 (9.7) 6.20</td>
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<tr>
<td>Most common adverse events, n (%)§</td>
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<tr>
<td>Infective pulmonary exacerbation of cystic fibrosis</td>
<td>95 (47.3) 181.13</td>
<td>44 (21.8) 64.88</td>
<td>225 (44.5) 37.40</td>
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<tr>
<td>Cough</td>
<td>77 (38.3) 113.08</td>
<td>34 (16.8) 38.93</td>
<td>212 (41.9) 30.63</td>
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<td>Headache</td>
<td>30 (14.9) 42.03</td>
<td>35 (17.3) 48.91</td>
<td>166 (32.8) 18.29</td>
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<tr>
<td>Oropharyngeal pain</td>
<td>25 (12.4) 26.02</td>
<td>20 (9.9) 26.95</td>
<td>146 (28.9) 16.85</td>
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<tr>
<td>Nasopharyngitis</td>
<td>26 (12.9) 34.03</td>
<td>22 (10.9) 29.95</td>
<td>135 (26.7) 17.04</td>
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<tr>
<td>Pyrexia</td>
<td>19 (9.5) 25.02</td>
<td>17 (8.4) 17.97</td>
<td>134 (26.5) 12.59</td>
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<td>Sputum increased</td>
<td>39 (19.4) 47.03</td>
<td>40 (19.8) 46.91</td>
<td>120 (23.7) 12.09</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>22 (10.9) 26.02</td>
<td>24 (11.9) 29.95</td>
<td>111 (21.9) 11.65</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>15 (7.5) 18.01</td>
<td>19 (9.4) 20.96</td>
<td>106 (20.9) 10.08</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (10.0) 22.02</td>
<td>9 (4.5) 8.98</td>
<td>104 (20.6) 11.21</td>
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<tr>
<td>COVID -19</td>
<td>0 (0) 0</td>
<td>0 (0) 0</td>
<td>99 (19.6) 7.70</td>
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### Parent Study 445-102†

<table>
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<tr>
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<th>ELX/TEZ/IVA N = 506</th>
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<tr>
<td><strong>Participants</strong></td>
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<tr>
<td>Nausea</td>
<td>14 (7.0)</td>
<td>16 (7.9)</td>
<td>84 (16.6)</td>
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<tr>
<td>Diarrhoea</td>
<td>14 (7.0)</td>
<td>26 (12.9)</td>
<td>80 (15.8)</td>
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<tr>
<td>Haemoptysis</td>
<td>28 (13.9)</td>
<td>11 (5.4)</td>
<td>78 (15.4)</td>
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<tr>
<td>Vaccination complication</td>
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<td><strong>Events/100PY</strong></td>
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<td>11.98</td>
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### Study 445-105 Week 144 Interim Analysis

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</tr>
<tr>
<td>Nausea</td>
<td>14 (7.0)</td>
<td>16 (7.9)</td>
<td>84 (16.6)</td>
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<tr>
<td>Diarrhoea</td>
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<tr>
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<td>Vaccination complication</td>
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<td><strong>Events/100PY</strong></td>
<td>15.97</td>
<td>31.94</td>
<td>6.64</td>
</tr>
<tr>
<td></td>
<td>11.98</td>
<td>12.03</td>
<td>9.52</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: ELX/TEZ/IVA=elexacaftor/tezacaftor/ivacaftor; PY=participant-years.

† A participant with multiple events within a category was counted only once in that category.

‡ The safety profile of ELX/TEZ/IVA was based on the 24-week, placebo-controlled, F/MF parent study.

‡ There was one death in the 144-week interim analysis of Study 445-105 which was due to accidental oxycodone toxicity and was not considered to be related to study drug.

§ The most common adverse events that occurred in ≥15% of participants in Study 445-102 or the interim analysis of Study 445-105; listing is according to the preferred term (Medical Dictionary for Regulatory Activities version 24.1).
Table 3. Secondary Efficacy Endpoints (*F508del-Minimal Function Genotypes*)

<table>
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<tr>
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<th>Parent Study 445-102 (F/MF Genotypes) Through Week 24</th>
<th>Study 445-105 at Extended Week 144 (F/MF Genotypes)</th>
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<td>Placebo N = 203</td>
<td>ELX/TEZ/IVA N = 200</td>
</tr>
<tr>
<td></td>
<td>ELX/TEZ/IVA N = 200</td>
<td>Placebo→ ELX/TEZ/IVA N = 203</td>
</tr>
<tr>
<td>Absolute change in percentage of predicted FEV₁ (95% CI), percentage points</td>
<td>−0.4 (−1.5 to 0.7)</td>
<td>13.9 (12.8 to 15.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change in sweat chloride concentration (95% CI), mmol/L</td>
<td>−0.4 (−2.2 to 1.4)</td>
<td>−42.2 (−44.0 to −40.4)</td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Absolute change in CFQ-R respiratory domain score (95% CI), points</td>
<td>−2.7 (−4.6 to -0.8)</td>
<td>17.5 (15.6 to 19.5)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Absolute change in BMI (95% CI), kg/m²</td>
<td>0.09 (−0.05 to 0.22)*</td>
<td>1.13 (0.99 to 1.26)*</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Estimated pulmonary exacerbation event rate per 48 weeks (95% CI)</td>
<td>0.98</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FEV₁ = forced expiratory volume in 1 second; F/MF = *F508del*- minimal function genotypes. Results are least-squares mean absolute change (95% CI) from baseline of the parent study, except for pulmonary exacerbation event rate.
* For BMI, parent study result represents mean absolute change from baseline at Week 24.

† Calculated from cumulative ELX/TEZ/IVA exposure in the parent study (Study 445-102) and in the extension study (Study 445-105).
Table 4. Secondary Efficacy Endpoints (*F508del- F508del Genotype*)

<table>
<thead>
<tr>
<th></th>
<th>Parent Study 445-103 (F/F Genotype) at Week 4</th>
<th>Study 445-105 at Extended Week 144 (F/F Genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEZ/IVA N = 52</td>
<td>TEZ/IVA (\rightarrow) ELX/TEZ/IVA N = 52</td>
</tr>
<tr>
<td>Absolute change in percentage of predicted FEV(_1) (95% CI), percentage points</td>
<td>0.4 (−1.4 to 2.3)</td>
<td>12.0 (9.5 to 14.5) n = 44</td>
</tr>
<tr>
<td>Absolute change in sweat chloride concentration (95% CI), mmol/L</td>
<td>1.7 (−1.9 to 5.3)</td>
<td>−53.4 (−57.7 to −49.0) n = 42</td>
</tr>
<tr>
<td>Absolute change in CFQ-R respiratory domain score (95% CI), points</td>
<td>−1.4 (−5.4 to 2.6)</td>
<td>16.0 (12.1 to 19.9) n = 45</td>
</tr>
<tr>
<td>Absolute change in BMI (95% CI), kg/m(^2)</td>
<td>−0.07 (−0.21 to 0.06)</td>
<td>0.53 (0.39 to 0.66) n = 44</td>
</tr>
<tr>
<td>Estimated pulmonary exacerbation event rate per 48 weeks (95% CI)*</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FEV\(_1\) = forced expiratory volume in 1 second; F/F = *F508del-F508del* genotype; NA = not
applicable; TEZ/IVA = tezacaftor/ivacaftor. Results are least-squares mean absolute change (95% CI) from baseline of the parent study, except for PEx event rate.

* Calculated from cumulative ELX/TEZ/IVA exposure in the parent study (Study 445-103) and in the extension study (Study 445-105).

† Participants in Study 445-103 had a 4-week TEZ/IVA run-in period prior to baseline.
Figure 1. Participant Disposition Diagram.

*Definition of abbreviations:* AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; OLE = open label extension; TEZ/IVA = tezacaftor/ivacaftor.
a One participant died during the study due to an AE of accidental oxycodone toxicity that was considered by the investigator to be unrelated to study drug.

b Other reasons for discontinuation included physician decision (n = 2), requirement of prohibited medication (n = 2), loss to follow-up (n = 1), non-compliance with study drug (n = 1), other non-compliance (n = 2) and not specified (n = 4).
**Figure 2. Absolute Change from Baseline in ppFEV$_1$, Sweat Chloride Concentration, CFQ-R Respiratory Domain Score and BMI in Participants with F/MF Genotypes by Study Visit**

Absolute change from baseline in ppFEV$_1$ (Panel a), sweat chloride concentration (Panel b), CFQ-R respiratory domain score (Panel c) and BMI (Panel d) in participants with F/MF genotypes by study visit, each based on a mixed-effects model for repeated measures (MMRM), are shown. Data presented are least squares means, with I-bars indicating standard error of the mean. White shading corresponds to the parent study (Study 445-102) and grey shading corresponds to the extension study. CFQ-R respiratory domain scores (Panel c) are normalised to a 100-point range, with higher scores indicating higher patient-reported quality of life with regards to respiratory symptoms. The minimal clinically important difference (MCID) for CFQ-R respiratory domain score is 4 points.

*Definition of abbreviations:* BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/MF = F508del-minimal function genotypes; ppFEV$_1$ = per cent predicted forced expiratory volume in 1 second; SwCl = sweat chloride.
b.
d.
Figure 3. Absolute Change from Baseline in ppFEV₁, Sweat Chloride Concentration, CFQ-R Respiratory Domain Score and BMI in Participants with the F/F Genotype by Study Visit

Absolute change from baseline in ppFEV₁ (Panel a), sweat chloride concentration (Panel b), CFQ-R respiratory domain score (Panel c) and BMI (Panel d) by study visit in participants with the F/F genotype, each based on a mixed-effects model for repeated measures (MMRM), are shown. Data presented are least squares means, with I-bars indicating standard error of the mean. White shading corresponds to the parent study (Study 445-103) and grey shading corresponds to the extension study. CFQ-R respiratory domain scores (Panel c) are normalised to a 100-point range, with higher scores indicating higher patient-reported quality of life with regards to respiratory symptoms. The minimal clinically important difference (MCID) for CFQ-R respiratory domain score is 4 points.

Definition of abbreviations: BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = F508del-F508del genotype; ppFEV₁ = per cent predicted forced expiratory volume in 1 second; SwCl = sweat chloride; TEZ/IVA = tezacaftor/ivacaftor.
b.

![Graph showing absolute change from baseline in SwCI concentration, mmol/L over weeks.](image)
Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in People With Cystic Fibrosis and at Least One F508del Allele: 144-Week Interim Results From a 192-Week Open-Label Extension Study

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**Drs. Ramsey and Griese contributed equally to this work.
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Supplementary Methods

The trial was conducted in accordance with the Declaration of Helsinki, local applicable laws and regulations and current Good Clinical Practice Guidelines as described by the International Council for Harmonisation.

Study Inclusion Criteria

- Participant (or his or her legally appointed and authorised representative) signed and dated an informed consent form, and, when appropriate, an assent form
- Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines and other study procedures
- Did not withdraw consent from a parent study
- Meets ≥1 of the following criteria:
  a. Completed study drug treatment in a parent study
  b. Had a study drug interruption(s) in a parent study but completed study visits up to the last scheduled visit of the Treatment Period of a parent study
- Willing to remain on a stable cystic fibrosis (CF) treatment regimen through completion of study participation

Study Exclusion Criteria

- History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the participant
- History of drug intolerance in a parent study that would pose an additional risk to the participant in the opinion of the investigator. (eg, participants with a history of allergy or hypersensitivity to the study drug.)

- Pregnant or nursing females. Females of childbearing potential must have had a negative pregnancy test at the Day 1 Visit before receiving the first dose of study drug.

- Current participation in an investigational drug trial (other than a parent study). Participation in a noninterventional trial (including observational studies, registry studies and studies requiring blood collections without administration of study drug) and screening for another Vertex study was permitted.

**Study Design**

Study VX17-445-105 is a Phase 3, multicentre, open-label, single-arm, extension study of the Phase 3 parent studies VX17-445-102 and VX17-445-103 that investigated elexacaftor (ELX) in combination with tezacaftor (TEZ) and ivacaftor (IVA) in participants with CF ≥12 years of age and either heterozygous for F508del and a minimal function mutation (FM/F) or homozygous for F508del (FF). The total study duration will be approximately 196 weeks from first dose of ELX/TEZ/IVA in this study and includes a 192-week treatment period followed by a 4-week safety follow-up period.

During the trial, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic led to implementation of a global protocol addendum that enabled in-home assessments to mitigate the varying prohibitions on travel and the limitation of on-site research procedures based on governmental and institutional restrictions. Through this global protocol addendum, safety measures were implemented to provide participants the opportunity to continue.
participating in this trial while minimising the risk of SARS-CoV-2 exposure through travel. Participant access to study drug therapy and collection of safety data were prioritised. These operational adjustments aligned with Health Authority guidance, ensuring the protection of participants, investigators and site personnel while maintaining compliance with Good Clinical Practice guidelines and minimising the impact of missed visits on study conduct. Implemented measures were based on country and local regulations, as well as site-level considerations, and included, as applicable, remote consent, shipment of the study drug, virtual study visits, in-home assessments (such as the Cystic Fibrosis Questionnaire–Revised) and remote monitoring. The clinical trial protocol, SARS-CoV-2–related protocol addendum and informed consent forms were approved by independent ethics committees for each region or site, as required by local regulations.

**Dosing**

All participants receive ELX/TEZ/IVA at the same dose level as was evaluated in the parent studies (Study 445-102 and Study 445-103).

**Adverse Events**

Study assessments including laboratory tests, electrocardiograms, physical examinations and vital signs were assessed, and those deemed to have clinically significant worsening from baseline were documented as an adverse event (AE). When possible, a clinical diagnosis for the study assessment was provided, rather than the abnormal test result alone (eg, urinary tract infection, anaemia). In the absence of a diagnosis, the abnormal study assessment itself was listed as the AE (eg, bacteria in urine or decreased haemoglobin).
An abnormal study assessment was considered clinically significant if the participant has ≥1 of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant was made by the investigator.

A laboratory value that is Grade 4 was automatically considered to be a serious AE. A Grade 4 laboratory value was a serious AE if the participant’s clinical status indicates a life-threatening AE.

All AEs were collected from the time the informed consent form is signed until the participant completes study participation. All participants were queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms were identified as one overall event or diagnosis. All AEs for enrolled participants were recorded in the case report form and source document. AEs for participants who were screened but not subsequently enrolled in the study were recorded only in the participant’s source documents. The following data were documented for each AE:

- Description of the event
- Classification of ‘serious’ or ‘non-serious’
- Date of first occurrence and date of resolution (if applicable)
- Severity
• Causal relationship of study drug(s)
• Action taken
• Outcome
• Concomitant medication or other treatment given

**Statistical Analysis**

A total of 506 participants were dosed in this extension study. With the number of participants exposed to ELX/TEZ/IVA, adverse events by preferred term that occur with a frequency of >1% can be ruled out with 95% confidence when zero events are observed in that preferred term. Furthermore, with over 400 participants exposed to ELX/TEZ/IVA for at least 24 weeks, the half-width of the 95% confidence interval for estimating cumulative incidence of pulmonary exacerbations of CF is <6%, assuming an observed incidence of 30%. The baseline value for the long-term safety analysis, unless otherwise specified, was the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA in the parent study or extension study, as applicable. The baseline value for all efficacy analyses was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of the study drug in the parent study. Missing data was assumed to be missing at random, and no imputation of missing data was performed.

The annualised mean rate of change in per cent predicted forced expiratory volume at 1 second (ppFEV₁) was estimated for participants with F/MF and F/F genotypes separately, as well as for all participants together (genotype groups pooled), using a linear mixed-effects model with the cumulative efficacy period ppFEV₁ values as the dependent variable. Data obtained in the first 21 days from the first ELX/TEZ/IVA dose were excluded. In addition, participants with <3 non-
missing percentage of predicted FEV$_1$ measurements or non-missing ppFEV$_1$ measurements spanning <180 days were excluded as well. The model included time from first dose divided by 336 as fixed effects, age at screening of parent study (<18 vs ≥18 years of age) and sex (male vs female) as covariates, and a random intercept and time as the random effects. The mixed model was estimated using the restricted maximum likelihood method and assuming an unstructured covariance matrix for the random effect errors. The degrees of freedom in the denominator were estimated based on the method of Kenward-Roger (1).
Supplementary Figure

Figure S1. Study Design

Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; F/F = F508del-F508del genotype; F/MF = F508del-minimal function genotypes; TEZ/IVA = tezacaftor/ivacaftor; qam = once in the morning; qpm = once in the evening.

* In the extension study, participants received ELX/TEZ/IVA at the same dose level that was evaluated in the parent studies.
## Supplementary Tables

### Table S1. Additional Baseline Characteristics of the Participants*

<table>
<thead>
<tr>
<th></th>
<th>Sub-Group of Participants From Parent Study 445-102 (F/MF Genotypes)</th>
<th>Sub-Group of Participants From Parent Study 445-103 (F/F Genotypes)</th>
<th>All Participants in Study 445-105</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N = 203</td>
<td>TEZ/IVA N = 52</td>
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<td><em>Pseudomonas aeruginosa</em> infection within 2 years prior to screening, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td>Positive</td>
<td>142 (70.0)</td>
<td>31 (59.6)</td>
<td>359 (70.9)</td>
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<td>Negative</td>
<td>61 (30.0)</td>
<td>21 (40.4)</td>
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<td>Prior use of dornase alfa, n (%)†</td>
<td></td>
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<tr>
<td>Yes</td>
<td>164 (80.8)</td>
<td>49 (94.2)</td>
<td>425 (84.0)</td>
</tr>
<tr>
<td>No</td>
<td>39 (19.2)</td>
<td>3 (5.8)</td>
<td>81 (16.0)</td>
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<td>Prior use of azithromycin, n (%)†</td>
<td></td>
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<tr>
<td>Yes</td>
<td>114 (56.2)</td>
<td>25 (48.1)</td>
<td>281 (55.5)</td>
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<tr>
<td>No</td>
<td>89 (43.8)</td>
<td>27 (51.9)</td>
<td>225 (44.5)</td>
</tr>
<tr>
<td>Prior use of inhaled antibiotic, n (%)†</td>
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<td></td>
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<td>Yes</td>
<td>133 (65.5)</td>
<td>28 (53.8)</td>
<td>314 (62.1)</td>
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<tr>
<td>No</td>
<td>70 (34.5)</td>
<td>24 (46.2)</td>
<td>192 (37.9)</td>
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<td>Prior use of any bronchodilator, n (%)†</td>
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<td>Yes</td>
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<td>47 (90.4)</td>
<td>477 (94.3)</td>
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<td>No</td>
<td>11 (5.4)</td>
<td>5 (9.6)</td>
<td>29 (5.7)</td>
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<td>Prior use of any inhaled bronchodilator, n (%)†</td>
<td>192 (94.6)</td>
<td>184 (93.9)</td>
<td>47 (90.4)</td>
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</tr>
<tr>
<td>No</td>
<td>11 (5.4)</td>
<td>12 (6.1)</td>
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<td>Prior use of any inhaled hypertonic saline, n (%)†</td>
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<td>147 (75.0)</td>
<td>43 (82.7)</td>
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<td>No</td>
<td>73 (36.0)</td>
<td>49 (25.0)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>BMI-for-age z-score, mean (SD) (participants aged ≤20 years)</td>
<td>−0.40 (0.98)</td>
<td>−0.37 (0.80)</td>
<td>−0.53 (0.91)</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: BMI = body mass index; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; TEZ/IVA = tezacaftor/ivacaftor.*

*Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the parent study treatment period. The open-label full analysis set is defined as all enrolled participants who received ≥1 dose of study drug in the open-label extension study.*

†*Includes medications started 56 days prior to the first dose of study drug in the treatment period.*
Table S2. Adverse Events Occurring in >5% of Participants

<table>
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<tr>
<th>Preferred Term</th>
<th>Study 445-102 Placebo N = 201</th>
<th></th>
<th>Study 445-102 ELX/TEZ/IVA N = 202</th>
<th></th>
<th>Study 445-105 ELX/TEZ/IVA N = 506</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with any AEs</td>
<td>193 (96.0)</td>
<td>1287.96</td>
<td>188 (93.1)</td>
<td>1096.01</td>
<td>500 (98.8)</td>
<td>586.55</td>
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<tr>
<td>Infective pulmonary exacerbation of cystic fibrosis</td>
<td>95 (47.3)</td>
<td>181.13</td>
<td>44 (21.8)</td>
<td>64.88</td>
<td>225 (44.5)</td>
<td>37.40</td>
</tr>
<tr>
<td>Cough</td>
<td>77 (38.3)</td>
<td>113.08</td>
<td>34 (16.8)</td>
<td>38.93</td>
<td>212 (41.9)</td>
<td>30.63</td>
</tr>
<tr>
<td>Headache</td>
<td>30 (14.9)</td>
<td>42.03</td>
<td>35 (17.3)</td>
<td>48.91</td>
<td>166 (32.8)</td>
<td>18.29</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>25 (12.4)</td>
<td>26.02</td>
<td>20 (9.9)</td>
<td>26.95</td>
<td>146 (28.9)</td>
<td>16.85</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>26 (12.9)</td>
<td>34.03</td>
<td>22 (10.9)</td>
<td>29.95</td>
<td>135 (26.7)</td>
<td>17.04</td>
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<td>Pyrexia</td>
<td>19 (9.5)</td>
<td>25.02</td>
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<td>17.97</td>
<td>134 (26.5)</td>
<td>12.59</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>39 (19.4)</td>
<td>47.03</td>
<td>40 (19.8)</td>
<td>46.91</td>
<td>120 (23.7)</td>
<td>12.09</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>22 (10.9)</td>
<td>26.02</td>
<td>24 (11.9)</td>
<td>29.95</td>
<td>111 (21.9)</td>
<td>11.65</td>
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<tr>
<td>Nasal congestion</td>
<td>15 (7.5)</td>
<td>18.01</td>
<td>19 (9.4)</td>
<td>20.96</td>
<td>106 (20.9)</td>
<td>10.08</td>
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<td>Fatigue</td>
<td>20 (10.0)</td>
<td>22.02</td>
<td>9 (4.5)</td>
<td>8.98</td>
<td>104 (20.6)</td>
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<td>COVID-19</td>
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<td>0</td>
<td>0 (0)</td>
<td>0</td>
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<td>Study 445-102 ELX/TEZ/IVA N = 202</td>
<td>Study 445-105 ELX/TEZ/IVA N = 506</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>Events/100PY</td>
<td>n (%)</td>
<td>Events/100PY</td>
<td>n (%)</td>
<td>Events/100PY</td>
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<td>Nausea</td>
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<td>16 (7.9)</td>
<td>15.97</td>
<td>84 (16.6)</td>
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<td>11.98</td>
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<td>Vaccination complication</td>
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<td>0 (0)</td>
<td>0</td>
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<td>Rhinorrhoea</td>
<td>6 (3.0)</td>
<td>7.01</td>
<td>17 (8.4)</td>
<td>18.97</td>
<td>69 (13.6)</td>
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<tr>
<td>Alanine aminotransferase increased</td>
<td>7 (3.5)</td>
<td>8.01</td>
<td>20 (9.9)</td>
<td>21.96</td>
<td>68 (13.4)</td>
<td>5.45</td>
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<td>Constipation</td>
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<td>68 (13.4)</td>
<td>5.64</td>
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<td>Arthralgia</td>
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<td>10.01</td>
<td>7 (3.5)</td>
<td>6.99</td>
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<tr>
<td>Sinusitis</td>
<td>8 (4.0)</td>
<td>8.01</td>
<td>11 (5.4)</td>
<td>14.97</td>
<td>66 (13.0)</td>
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<td>23.96</td>
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<td>5.76</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>4 (2.0)</td>
<td>4.00</td>
<td>19 (9.4)</td>
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<td>4.82</td>
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<tr>
<td>Blood creatine phosphokinase increased</td>
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<td>9.01</td>
<td>19 (9.4)</td>
<td>19.96</td>
<td>65 (12.8)</td>
<td>5.57</td>
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<td>59 (11.7)</td>
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<td>59 (11.7)</td>
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<td>57 (11.3)</td>
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<td>14 (6.9)</td>
<td>15.97</td>
<td>53 (10.5)</td>
<td>4.07</td>
</tr>
<tr>
<td>Preferred Term</td>
<td>Study 445-102 Placebo N = 201</td>
<td>Study 445-102 ELX/TEZ/IVA N = 202</td>
<td>Study 445-105 ELX/TEZ/IVA N = 506</td>
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<tr>
<td></td>
<td>n (%) Events/100PY</td>
<td>n (%) Events/100PY</td>
<td>n (%) Events/100PY</td>
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<td>Rash</td>
<td>9 (4.5) 12.01</td>
<td>19 (9.4) 24.95</td>
<td>52 (10.3) 4.57</td>
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<tr>
<td>Productive cough</td>
<td>16 (8.0) 17.01</td>
<td>12 (5.9) 11.98</td>
<td>50 (9.9) 4.76</td>
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<tr>
<td>Rhinitis</td>
<td>11 (5.5) 14.01</td>
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<td>49 (9.7) 6.70</td>
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<td>47 (9.3) 3.26</td>
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<td>44 (8.7) 4.01</td>
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<tr>
<td>Bacterial test positive</td>
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<td>5 (2.5) 4.99</td>
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<td>36 (7.1) 2.69</td>
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<td>7 (3.5) 6.99</td>
<td>36 (7.1) 2.82</td>
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<td>3 (1.5) 2.99</td>
<td>36 (7.1) 2.76</td>
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<td>0 (0) 0</td>
<td>33 (6.5) 2.44</td>
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<td>3 (1.5) 2.99</td>
<td>32 (6.3) 2.63</td>
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<td>0 (0) 0</td>
<td>0 (0) 0</td>
<td>32 (6.3) 2.07</td>
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<td></td>
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<td>Pain in extremity</td>
<td>1 (0.5) 1.00</td>
<td>1 (0.5) 1.00</td>
<td>31 (6.1) 2.63</td>
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<tr>
<td>Preferred Term</td>
<td>Study 445-102 Placebo N = 201</td>
<td>Study 445-102 ELX/TEZ/IVA N = 202</td>
<td>Study 445-105 ELX/TEZ/IVA N = 506</td>
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<td>Events/100PY</td>
<td>n (%)</td>
<td>Events/100PY</td>
<td>n (%)</td>
<td>Events/100PY</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
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<td>2.00</td>
<td>10 (5.0)</td>
<td>10.98</td>
<td>30 (5.9)</td>
<td>2.82</td>
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<td>2.00</td>
<td>9 (4.5)</td>
<td>8.98</td>
<td>30 (5.9)</td>
<td>2.19</td>
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<td>2.00</td>
<td>6 (3.0)</td>
<td>5.99</td>
<td>29 (5.7)</td>
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<tr>
<td>Respiration abnormal</td>
<td>4 (2.0)</td>
<td>4.00</td>
<td>9 (4.5)</td>
<td>9.98</td>
<td>29 (5.7)</td>
<td>2.57</td>
</tr>
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<td>Wheezing</td>
<td>2 (1.0)</td>
<td>2.00</td>
<td>6 (3.0)</td>
<td>6.99</td>
<td>29 (5.7)</td>
<td>2.63</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.5)</td>
<td>1.00</td>
<td>3 (1.5)</td>
<td>2.99</td>
<td>28 (5.5)</td>
<td>2.07</td>
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<td>Myalgia</td>
<td>5 (2.5)</td>
<td>5.00</td>
<td>5 (2.5)</td>
<td>4.99</td>
<td>28 (5.5)</td>
<td>2.07</td>
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<tr>
<td>Viral upper respiratory tract infection</td>
<td>4 (2.0)</td>
<td>4.00</td>
<td>9 (4.5)</td>
<td>11.98</td>
<td>28 (5.5)</td>
<td>2.44</td>
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<td>Abdominal distension</td>
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<td>4.00</td>
<td>5 (2.5)</td>
<td>6.99</td>
<td>27 (5.3)</td>
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<td>2.00</td>
<td>0 (0)</td>
<td>0</td>
<td>27 (5.3)</td>
<td>2.00</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years;

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Table S3. Summary of Most Common Adverse Events (>15% at Week 144) at Weeks 48, 96, and 144

<table>
<thead>
<tr>
<th>Most common adverse events*, n (%)</th>
<th>Study 445-105 Week 48 Interim Analysis</th>
<th>Study 445-105 Week 96 Interim Analysis</th>
<th>Study 445-105 Week 144 Interim Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELX/TEZ/IVA N = 506</td>
<td>ELX/TEZ/IVA N = 506</td>
<td>ELX/TEZ/IVA N = 506</td>
</tr>
<tr>
<td>Mean Exposure = 37.2 Weeks</td>
<td></td>
<td>Mean Exposure = 105.7 Weeks</td>
<td>Mean Exposure = 151.1 Weeks</td>
</tr>
<tr>
<td>Participants</td>
<td>Events/100PY</td>
<td>Participants</td>
<td>Events/100PY</td>
</tr>
<tr>
<td>Infected pulmonary exacerbation of cystic fibrosis</td>
<td>127 (25.1)</td>
<td>49.60</td>
<td>191 (37.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>118 (23.3)</td>
<td>44.26</td>
<td>183 (36.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>66 (13.0)</td>
<td>24.93</td>
<td>124 (24.5)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>74 (14.6)</td>
<td>25.69</td>
<td>132 (26.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>69 (13.6)</td>
<td>21.62</td>
<td>114 (22.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>44 (8.7)</td>
<td>12.46</td>
<td>95 (18.8)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>63 (12.5)</td>
<td>20.60</td>
<td>100 (19.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>60 (11.9)</td>
<td>18.31</td>
<td>99 (19.6)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>48 (9.5)</td>
<td>16.79</td>
<td>81 (16.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (10.1)</td>
<td>16.28</td>
<td>80 (15.8)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>0 (0)</td>
<td>0</td>
<td>15 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Study 445-105 Week 48 Interim Analysis</td>
<td>Study 445-105 Week 96 Interim Analysis</td>
<td>Study 445-105 Week 144 Interim Analysis</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>ELX/TEZ/IVA</td>
<td>N = 506</td>
<td>N = 506</td>
<td>N = 506</td>
</tr>
<tr>
<td>Mean Exposure = 37.2 Weeks</td>
<td></td>
<td>Mean Exposure = 105.7 Weeks</td>
<td>Mean Exposure = 151.1 Weeks</td>
</tr>
<tr>
<td>Participants</td>
<td>Events/100PY</td>
<td>Participants</td>
<td>Events/100PY</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (6.3)</td>
<td>62 (12.3)</td>
<td>7.25</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>38 (7.5)</td>
<td>65 (12.8)</td>
<td>7.07</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>36 (7.1)</td>
<td>58 (11.5)</td>
<td>11.10</td>
</tr>
<tr>
<td>Vaccination complication</td>
<td>0 (0)</td>
<td>16 (3.2)</td>
<td>1.88</td>
</tr>
</tbody>
</table>

* The most common adverse events that occurred in ≥15% of participants in the Week 144 interim analysis of Study 445-105; listing is according to the preferred term (Medical Dictionary for Regulatory Activities version 24.1).
Table S4. Liver Function Test Enzyme Elevations and Adverse Events of Elevated Transaminases

<table>
<thead>
<tr>
<th>Study 445-102 Placebo</th>
<th>Study 445-102 ELX/TEZ/IVA</th>
<th>Study 445-105 ELX/TEZ/IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong> = 201</td>
<td><strong>N</strong> = 202</td>
<td><strong>N</strong> = 506</td>
</tr>
<tr>
<td><strong>Participants (%)</strong></td>
<td><strong>Events/100PY</strong>$^$</td>
<td><strong>Participants (%)</strong></td>
</tr>
<tr>
<td><strong>ALT or AST, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 × ULN</td>
<td>11 (5.5)</td>
<td>16 (7.9)</td>
</tr>
<tr>
<td>&gt;5 × ULN</td>
<td>3 (1.5)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>&gt;8 × ULN</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td><strong>ALT or AST and total bilirubin, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt;3 × ULN and total bilirubin &gt;2 × ULN</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td><strong>Elevated transaminase levels adverse event group term$^\ddagger$ — n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event of elevated transaminase levels</td>
<td>8 (4.0)</td>
<td>22 (10.9)</td>
</tr>
<tr>
<td>Serious adverse events of elevated transaminase levels</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adverse events of elevated transaminase levels leading to treatment interruption</td>
<td>3 (1.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Adverse events of elevated transaminase levels leading to treatment discontinuation</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Time-to-onset of first event, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>--------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Min, Max</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Duration of events, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Min, Max</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; NA = not applicable; PY = participant-years; ULN = upper limit of normal.

* For the liver function test threshold analyses, each percentage is calculated as \( \frac{n}{N_1} \times 100 \), where the numerator ‘\( n \)’ is the number of participants in the post-Triple-Combination-safety-baseline meeting the indicated threshold, and the denominator (\( N_1 \)) is the number of participants with \( \geq 1 \) non-missing measurement during the open-label safety period. For ‘ALT or AST’, counts are based on the highest value of either test during the treatment-emergent period for each participant. A participant whose highest value is \( > 5 \times \text{ULN} \) is also counted as \( > 3 \times \text{ULN} \). A participant whose highest value is \( > 8 \times \text{ULN} \) is also counted as \( > 3 \times \text{ULN} \) and \( > 5 \times \text{ULN} \).

† Two participants (0.4%) in Study 445-105 had ALT or AST \( > 3 \times \text{ULN} \) with concurrent newly occurred bilirubin \( > 2 \times \text{ULN} \). In a third participant, the ALT or AST \( > 3 \times \text{ULN} \) and bilirubin \( > 2 \times \text{ULN} \) elevations were not concurrent.

‡ Group term of ‘elevated transaminase events’ included multiple preferred terms.

§ Events per 100 participant-years was calculated by dividing the number of events by the total duration of the safety analysis period in 100 participant-years. 1 year = 48 weeks = 336 days.
## Table S5. Summary of Rash Events*

<table>
<thead>
<tr>
<th></th>
<th>Study 445-102 Placebo</th>
<th>Study 445-102 ELX/TEZ/IVA</th>
<th>Study 445-105 ELX/TEZ/IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 201</td>
<td>N = 202</td>
<td>N = 506</td>
</tr>
<tr>
<td>Any rash event, n (%)</td>
<td>13 (6.5)</td>
<td>22 (10.9)</td>
<td>82 (16.2)</td>
</tr>
<tr>
<td>Male, n/N1 (%)†</td>
<td>5/105 (4.8)</td>
<td>6/104 (5.8)</td>
<td>33/255 (12.9)</td>
</tr>
<tr>
<td>Female, n/N1 (%)†</td>
<td>8/96 (8.3)</td>
<td>16/98 (16.3)</td>
<td>49/251 (19.5)</td>
</tr>
<tr>
<td>Serious rash event, n (%)</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Concomitant hormone therapy use, n/N1 (%)‡</td>
<td>3/32 (9.4)</td>
<td>8/40 (20.0)</td>
<td>25/122 (20.5)</td>
</tr>
<tr>
<td>No concomitant hormone therapy use, n/N1 (%)‡</td>
<td>5/64 (7.8)</td>
<td>8/58 (13.8)</td>
<td>24/129 (18.6)</td>
</tr>
<tr>
<td>Time-to-onset of first event, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>51.2 (51.7)</td>
<td>36.7 (44.6)</td>
<td>241.2 (268.7)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>1, 157</td>
<td>5, 157</td>
<td>1, 1120</td>
</tr>
<tr>
<td>Duration of events, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.0 (14.4)</td>
<td>11.5 (17.0)</td>
<td>21.5 (41.9)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>2, 61</td>
<td>1, 92</td>
<td>1, 254</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: ELX/TEZ/IVA = eluxacaftor/tezacaftor/ivacaftor; PY = participant-years.

* When summarising numbers and percentages of participants, a participant with multiple events within a category is counted only once in that category. Group term of ‘rash events’ includes terms of rash (eg, rash, rash erythematous, rash maculopapular, rash papular, skin exfoliation and urticaria).
† For analyses stratified by sex and concomitant hormone therapy use, each percentage is calculated as \((n/N_1) \times 100\), where the numerator ‘n’ is the number of participants in the specified subgroup (ie, sex or concomitant hormone therapy use category) with rash events, and the denominator (N_1) is the total number of participants in the specified subgroup.

‡ Hormone therapy included oestrogens and progestogens based on the standard drug groupings using the World Health Organization Drug Dictionary, version March 2021, format B3.
Table S6. Adverse Events of Blood Creatine Phosphokinase Increased

<table>
<thead>
<tr>
<th></th>
<th>Study 445-102 Placebo</th>
<th>Study 445-102 ELX/TEZ/IVA</th>
<th>Study 445-105 ELX/TEZ/IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants (%)</td>
<td>Events/100PY</td>
<td>Participants (%)</td>
</tr>
<tr>
<td>Any adverse event of blood</td>
<td>9 (4.5)</td>
<td>9.01</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>creatine phosphokinase increased, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events of blood</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>creatine phosphokinase increased, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Definition of abbreviations: ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years.*
Table S7. Summary of Blood Pressure Data

<table>
<thead>
<tr>
<th></th>
<th>Study 445-102 Placebo</th>
<th>Study 445-102 ELX/TEZ/IVA</th>
<th>Study 445-105 ELX/TEZ/IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 201</td>
<td>N = 202</td>
<td>N = 506</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP — mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP — mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent study baseline</td>
<td>201</td>
<td>202</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>113.7 (12.1)</td>
<td>113.4 (11.7)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>69.7 (9.4)</td>
<td>69.4 (9.7)</td>
<td>–</td>
</tr>
<tr>
<td>Change at Week 24</td>
<td>198</td>
<td>198</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>−0.1 (12.4)</td>
<td>3.1 (10.8)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>0.3 (8.9)</td>
<td>1.9 (10.2)</td>
<td>–</td>
</tr>
<tr>
<td>Change at Extended Week 144</td>
<td>–</td>
<td>–</td>
<td>424</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>3.9 (12.5)</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>2.6 (9.0)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations:* ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Baseline was the parent study baseline, defined as the most recent non-missing measurement before the first dose of study drug in the parent study treatment period.
### Table S8. Adverse Events Related to Blood Pressure*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants (%)</td>
<td>Events/100PY</td>
<td>Participants (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.5)</td>
<td>1.00</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>1 (0.5)</td>
<td>1.00</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Diastolic hypertension</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blood pressure diastolic increased</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertensive urgency†</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*All adverse events related to blood pressure were nonserious and did not require change in ELX/TEZ/IVA dosing; 7 participants required medication for elevated blood pressure.

† There was 1 serious AE of hypertensive urgency in a 52-year-old female with type 2 diabetes, chronic kidney disease and a history of hypertension. After approximately 2.5 years in Study 105, she was diagnosed with essential hypertension and cardiomyopathy that was assessed as not related to ELX/TEZ/IVA, and there was no change in study drug.

**Definition of abbreviations:** ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; PY = participant-years.
Table S9. Annualised Rate of Change in ppFEV₁*

<table>
<thead>
<tr>
<th></th>
<th>Participants With F/MF Genotypes</th>
<th>Participants With F/F Genotype</th>
<th>All Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of participants</td>
<td>392</td>
<td>105</td>
<td>497</td>
</tr>
<tr>
<td>Estimate of slope (standard error) per 48 weeks, percentage points</td>
<td>0.08 (0.11)</td>
<td>0.03 (0.18)</td>
<td>0.07 (0.10)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(-0.14 to 0.30)</td>
<td>(-0.33 to 0.39)</td>
<td>(-0.12 to 0.26)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: F/F = F508del-F508del genotype; F/MF = F508del-minimal function genotypes; ppFEV₁ = per cent predicted forced expiratory volume in 1 second.

* Based on the cumulative efficacy period in Study 445-102, Study 445-103 and Study 445-105, up to approximately 151 weeks of follow-up. Includes only post-baseline measurements beyond 21 days from treatment initiation and only participants having ≥3 non-missing ppFEV₁ records spanning ≥180 days.
Table S10. Incidence of depression and depression-related adverse events in ELX/TEZ/IVA pivotal phase 3 trial (Study 445-102) and in the ELX/TEZ/IVA pooled clinical trial data*

<table>
<thead>
<tr>
<th>Event</th>
<th>Exposure-adjusted event rate (per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pivotal Study 445-102</td>
</tr>
<tr>
<td></td>
<td>Placebo N=201 100 PY</td>
</tr>
<tr>
<td>Any Depression AEs (SMQ)</td>
<td>5.0</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1.00</td>
</tr>
<tr>
<td>Completed suicide</td>
<td>0</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: AE = adverse event; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor and ivacaftor; PY = participant years.
*Placebo column includes data from participants who received placebo in the following 10 completed CFTR modulator studies: 445-102, 659-102, 809-103, 809-104, 661-106, 661-107, and 770-102 (studies in participants 12 years of age and older) and 445-116, 809-109, and 770-103 (studies in participants 6 through 11 years of age).

References

**Data Sharing Statement**

Vertex is committed to advancing medical science and improving participant health. This 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 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.