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Long-Term Safety and Efficacy of Tezacaftor/Ivacaftor in People With Cystic Fibrosis ≥12 Years of Age Homozygous or Heterozygous for *F508del-CFTR* From an Open-label Extension Study

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ABSTRACT (Limit: 250; currently: 393)

Background: Tezacaftor/ivacaftor is an approved CFTR modulator shown to be efficacious and generally safe and well tolerated over 8 to 24 weeks in Phase 3 clinical studies in participants ≥12 years of age with CF homozygous for the *F508del-CFTR* mutation (*F/F*; study 661-106) or heterozygous for the *F508del-CFTR* mutation and a residual function mutation (*F*/RF; study 661-108). Longer-term (>24 weeks) safety and efficacy of tezacaftor/ivacaftor has not been evaluated in clinical studies. Here, we present results of study 661-110, a 96-week open-label extension study that evaluated long-term safety, tolerability, and efficacy of tezacaftor/ivacaftor in participants ≥12 years of age homozygous or heterozygous for the *F508del-CFTR* mutation.

Methods: Participants were ≥12 years of age, had CF, were homozygous or heterozygous for *F508del-CFTR*, and completed one of several studies of tezacaftor/ivacaftor. Participants received tezacaftor 100 mg once daily and ivacaftor 150 mg once every 12 hours for up to 96 weeks. The primary endpoint of study 661-110 was safety and tolerability. Secondary endpoints were changes in lung function, nutritional parameters, and respiratory symptom scores; pulmonary exacerbations; and pharmacokinetic parameters. A post hoc analysis evaluated the rate of lung function decline in *F/F* participants who received up to 120 weeks of tezacaftor/ivacaftor in studies 661-106 (*F/F*) and/or 661-110 compared with a matched cohort of CFTR modulator–untreated historical *F/F* controls from the Cystic Fibrosis Foundation Patient Registry. (ClinicalTrials.gov identifier, NCT02565914)

Findings: This study was conducted from August 31, 2015, to May 31, 2019. The safety profile of tezacaftor/ivacaftor in study 661-110 (n=1042) was consistent with CF manifestations and with the safety profiles of the parent studies. Twenty-two participants (2·1%) had TEAEs leading to discontinuation; 351 (33·7%) had serious TEAEs. *F/F* (n=459) and *F*/RF (n=226) participants

beginning tezacaftor/ivacaftor in study 661-110 had improvements in efficacy endpoints consistent with parent studies; improvements in tezacaftor/ivacaftor groups observed in the parent studies were generally maintained in study 661-110. The annualized rate of lung function decline was 61·5% (95% CI, 35·8 to 86·1) lower in tezacaftor/ivacaftor–treated *F*/*F* participants versus untreated matched historical controls.

Interpretation: Tezacaftor/ivacaftor was generally safe, well tolerated, and efficacious for up to 120 weeks. Rate of lung function decline was significantly reduced in *F/F* participants, consistent with CF disease modification. Our results support the clinical benefit of long-term tezacaftor/ivacaftor treatment for people ≥12 years of age with CF with *F/F* or *F*/RF genotypes.

Funding: Vertex Pharmaceuticals Incorporated.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed on September 11, 2020, using the terms "ivacaftor" or "VX-770" and "tezacaftor" or "VX-661", with no restrictions on publication date or language. We retrieved four relevant clinical trial publications: a Phase 3 trial of tezacaftor/ivacaftor (TEZ/IVA; up to 24 weeks) in participants ≥12 years of age with cystic fibrosis (CF) homozygous for the *F508del-CFTR* mutation (study 661-106; *F*/*F* participants), a Phase 3 trial of TEZ/IVA (up to 12 weeks) in participants ≥12 years of age with CF heterozygous for the *F508del-CFTR* mutation and a minimal function mutation (study 661-107; *F*/MF participants), a Phase 3 trial of TEZ/IVA (up to 8 weeks) in participants ≥12 years of age with CF heterozygous for the *F508del-CFTR* mutation and a residual function mutation (study 661-108; *F*/RF participants), and a Phase 3b

trial of TEZ/IVA (up to 56 days) in participants ≥12 years of age with CF homozygous for the *F508del-CFTR* mutation who discontinued lumacaftor/ivacaftor due to treatment-related respiratory signs or symptoms (study 661-114; *F/F* participants). The clinical efficacy and safety of TEZ/IVA in people ≥12 years of age with CF was established based on the results of Phase 3 trials 661-106 and 661-108.

Added value of this study

The safety and efficacy of longer-term (>24 weeks) TEZ/IVA treatment has not been previously evaluated in clinical studies. Study 661-110 was a 96-week open-label extension study designed to assess long-term safety, tolerability, and efficacy of TEZ/IVA in participants ≥12 years of age homozygous or heterozygous for the *F508del-CFTR* mutation who completed one of several pivotal parent studies of TEZ/IVA, including studies 661-106 (*F/F*) and 661-108 (*F*/RF). The rate of lung function decline in TEZ/IVA-treated participants has not been previously evaluated. A post hoc analysis was conducted to evaluate rate of lung function decline in *F/F* participants who received up to 120 weeks of TEZ/IVA in studies 661-106 (*F*/*F*) and 661-110 compared with a matched cohort of CF transmembrane conductance regulator (CFTR) modulator–untreated historical *F/F* controls from the Cystic Fibrosis Foundation Patient Registry. We observed that up to 120 weeks of TEZ/IVA treatment was generally safe and well tolerated, with a safety profile consistent with that observed in the parent studies. The observed benefits of TEZ/IVA on lung function, nutritional status, and pulmonary exacerbation rates were generally maintained for up to 120 weeks of treatment. Post hoc analysis demonstrated that TEZ/IVA treatment was associated with a significant reduction in lung function decline in *F*/*F* participants compared with CFTR modulator–untreated historical *F/F* controls.

Implications of all the available evidence

Study 661-110 showed that TEZ/IVA was generally safe and well tolerated for up to 120 weeks, with a safety profile consistent with that observed in the parent studies. Our results support the clinical value of long-term TEZ/IVA treatment for people ≥12 years of age with CF with an *F*/*F* or *F*/RF genotype. The rate of lung function decline was significantly reduced in *F*/*F* participants taking TEZ/IVA, consistent with modification of the course of CF disease.

INTRODUCTION

Cystic fibrosis (CF) is a life-shortening, multisystem genetic disease affecting approximately 85,000 people worldwide.[1] CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene that reduce the quantity and/or function of the CFTR protein (an anion channel) on epithelial cell surfaces.[1,2] The *F508del-CFTR* mutation, the most common *CFTR* mutation, severely impairs the processing and trafficking of the CFTR protein to the epithelial cell surface and the function of the CFTR protein that reaches the cell surface.[2,3] People with two copies of the *F508del-CFTR* mutation (*F/F* genotype) develop severe multisystem disease with progressive loss of lung function.[4,5] Approximately 5% of people with CF (pwCF) have *CFTR* mutations resulting in residual CFTR anion transport due to partially retained CFTR expression and function on epithelial cell surfaces.[4,6] However, pwCF possessing residual function (RF) mutations still develop multisystem manifestations of CF and severe disease.[4,7] RF mutations are most commonly inherited with the *F508del-CFTR* mutation (*F/*RF genotype) on the other allele.[8] Compared with pwCF who are homozygous for *F508del-CFTR* (*F/F*), those with *F/*RF genotypes generally have slower disease progression and are more likely to be pancreatic sufficient and have sweat chloride concentrations <90 mmol/L, indicative of partially preserved CFTR activity.[6,9-11] Nevertheless, pwCF with *F/*RF genotypes develop lung disease with increasing age and die prematurely.[7]

Small-molecule CFTR modulator (CFTRm) therapies have been developed for pwCF that target the underlying CFTR dysfunction.[12-15] CFTR correctors (e.g., lumacaftor, tezacaftor, and elexacaftor) bind to the protein product of the *F508del-CFTR* mutation to improve processing of the mutant, misfolded protein and its trafficking to cell surfaces.[13-15] CFTR potentiators (e.g.,

ivacaftor [IVA]) increase the open probability of the CFTR channels present on cell surfaces.[12] The first two approved CFTRm therapies, IVA and lumacaftor/ivacaftor combination therapy (LUM/IVA), were shown to modify the progression of CF disease in their indicated populations compared with matched CFTRm-untreated controls in the US CF Foundation Patient Registry (CFFPR).[16-19] Both IVA and LUM/IVA treatments reduced lung function decline in their indicated populations.[16-19] In addition, IVA treatment was associated with reductions in mortality, lung transplant, pulmonary exacerbation, and hospitalization rates and improvements in nutritional status.[16,17] Tezacaftor/ivacaftor combination therapy (TEZ/IVA) was shown to be effective and generally safe and well tolerated in 24- or 8-week Phase 3 clinical studies (EVOLVE or EXPAND, respectively) in participants ≥12 years of age with CF who have *F/F* or *F*/RF genotypes, respectively.[20,21] TEZ/IVA is approved to treat pwCF with TEZ/IVA-responsive mutations who are ≥6 years of age in the United States and ≥12 years of age in other regions.[22,23] The safety and efficacy of longer-term (>24 weeks) TEZ/IVA use has not been evaluated in clinical studies.

Here, we report the findings of a 96-week extension study (661-110; EXTEND) that assessed the long-term safety and efficacy of TEZ/IVA treatment in participants ≥12 years of age with CF homozygous or heterozygous for the *F508del-CFTR* mutation who completed a placebo (PBO) and/or IVA-controlled parent study of TEZ/IVA. A post hoc analysis was also conducted to evaluate the rate of lung function decline in *F/F* participants who received up to 120 weeks of TEZ/IVA in studies 661-106 (*F/F*) and/or 661-110, compared with a matched cohort of CFTRm-untreated historical *F/F* controls from the CFFPR. This analysis was not possible in the *F*/RF cohort due to an insufficient sample size.

METHODS

Study Design and Eligibility Criteria

Study 661-110 (ClinicalTrials.gov identifier, NCT02565914) was a 96-week, Phase 3, multicenter, open-label study (**Figure 1**) in participants ≥12 years of age with CF homozygous or heterozygous for the *F508del-CFTR* mutation who completed one of several studies of TEZ/IVA. Participants who completed study-drug treatment (TEZ/IVA, IVA alone, or PBO) during the treatment period in parent studies 661-103 (NCT02070744; *F/F*), 661-106 (NCT02347657; *F/F*),[20] 661-107 (NCT02516410; *F*/MF [heterozygous for *F508del-CFTR* and a minimal function *CFTR* mutation]),[24] 661-108 (NCT02392234; *F*/RF),[21] 661-109 (NCT02412111; *F*/gating or *F/R117H* [heterozygous for *F508del-CFTR* and either a *CFTR* gating or a *R117H-CFTR* mutation]), or 661-111 (NCT02508207; *F/F*) were eligible for study 661-110. Study 661-103 (*F/F*) was a Phase 2, randomized, PBO-controlled, 12-week study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of TEZ/IVA in participants ≥18 years of age with CF. Study 661-106 (*F/F*) was a Phase 3, randomized, PBO-controlled, 24-week study of the efficacy and safety of TEZ/IVA in participants ≥12 years of age with CF.[20] Study 661-107 (*F*/MF) was a Phase 3, randomized, PBO-controlled, 12-week study of the efficacy and safety of TEZ/IVA in participants ≥12 years of age with CF.[24] Study 661-108 (*F*/RF) was a Phase 3, randomized, PBO- and IVA-controlled, crossover study (2 8-week interventional periods) of the efficacy and safety of TEZ/IVA in participants ≥12 years of age with CF.[21] Study 661-109 (*F*/gating and *F/R117H*) was a Phase 3, randomized, IVA-controlled, 8-week study of the efficacy and safety of TEZ/IVA in participants ≥12 years of age with CF. Study 661-111 (*F/F*) was a Phase 2, randomized, PBO-controlled, 29-day exploratory study of the effects of

TEZ/IVA on lung and extrapulmonary systems in participants ≥18 years of age with CF. Efficacy in 661-110 was reported only in participants with an *F/F* or *F*/RF genotype who enrolled from study 661-106 (*F/F*) or 661-108 (*F*/RF); eligible RF mutations for 661-108 (*F*/RF) are reported in the **appendix (p 9)**. Participants from studies 661-107 (*F*/MF) and 661-109 (*F*/gating or *F*/R117H) were discontinued early from study 661-110 because these parent studies did not meet their primary endpoint; accordingly, efficacy was not assessed in these participants in 661-110. Efficacy endpoints were assessed in participants who transitioned from studies 661-103 (*F/F*) and 661-111 (*F/F*); however, the sample sizes were small and results from these participants are not reported here. Exclusion criteria included history of any comorbidity (e.g., cirrhosis with portal hypertension) that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering TEZ/IVA to participants. Full eligibility criteria are reported in the **appendix (pp 10-11)**.

Participants received TEZ 100 mg once daily and IVA 150 mg every 12 hours for up to 96 weeks. Procedural methods on the transition to study 661-110, the timing of assessments, and treatment compliance are reported in the **appendix (p 7)**.

Objectives and Endpoints

The primary objective of study 661-110 was to evaluate the long-term safety and tolerability of TEZ/IVA in participants with CF homozygous or heterozygous for the *F508del-CFTR* mutation. The primary endpoint was safety and tolerability based on adverse events (AEs), ophthalmologic examinations (in participants <18 years of age at the date of informed consent/assent in the

parent study), clinical laboratory values (serum chemistry, hematology, coagulation, lipids, vitamins, and urinalysis), standard digital electrocardiograms, vital signs, and pulse oximetry.

The secondary objective was to evaluate the long-term efficacy of TEZ/IVA. Secondary endpoints were absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$); relative change from baseline in $ppFEV_1$; number of pulmonary exacerbations (PEx); absolute change from baseline in body mass index (BMI), BMI *z* score (in participants <20 years of age), CF Questionnaire–Revised (CFQ-R) respiratory domain score, body weight, body weight *z* score (in participants <20 years of age), and height *z* score (in participants <20 years of age); time to first PEx; and pharmacokinetics parameters of TEZ, M1-TEZ, IVA, and M1-IVA.

A post hoc analysis of the rate of lung function decline was conducted on *F/F* participants treated with TEZ/IVA for up to 120 weeks in studies 661-106 (*F/F*) and/or 661-110 and a propensity score–matched cohort of CFTRm-untreated *F/F* historical controls ≥12 years of age using data from the CFFPR from 2012 through 2014, prior to commercial availability of the first CFTRm for *F/F* pwCF in the United States. To be eligible for the analysis, both TEZ/IVA–treated and historical control participants had to have at least three consecutive lung function measurements spanning ≥6 months.

Statistical Analyses

This study did not have a target sample size; a convenience sample was used (see the **appendix p 7** for additional information). The Safety Set included all participants, regardless of their

genotype and from all 6 parent studies, who received at least one dose of study drug at any time during the 96-week treatment period of study 661-110. The Full Analysis Set (FAS) included all participants who received at least one dose of study drug at any time during the 96-week treatment period of study 661-110 and had *F*/*F* or *F*/RF genotypes. There were two efficacy sets: the 106/110 Efficacy Set (*F/F*) included all participants in the FAS who transitioned from study 661-106 (*F/F*), and the 108/110 Efficacy Set (*F*/RF) included all participants in the FAS who transitioned from study 661-108 (*F*/RF). PEx were analyzed using the 106/110 PEx Analysis Set (*F/F*) or the 108/110 PEx Analysis Set (*F*/RF), which included all participants receiving TEZ/IVA in either studies 661-106 (*F/F*) or 661-108 (*F*/RF), respectively, and/or 661-110. For the PEx analysis in participants transitioning from study 661-108 (*F*/RF), only PEx data from period 2 of study 661-108 (*F*/RF) were pooled with PEx data from study 661-110 because there was an 8-week TEZ/IVA washout between the two treatment periods in study 661-108 (*F*/RF).

Continuous variables were summarized using descriptive statistics: number of participants, mean, SD, median, minimum, and maximum. Categorical variables were summarized using counts and percentages. Continuous efficacy endpoints were analyzed using a mixed-effects model for repeated measures. Wang and Hankinson (W-H) equations were used to calculate $ppFEV_1$ for change-from-baseline analyses.[25,26] The number of PEx was analyzed using a negative binomial regression model, and time to first PEx was analyzed using the Kaplan-Meier approach. Statistical comparisons of PEx rates in study 661-110 versus those in the parent studies were not conducted because PEx events in the parent studies in participants receiving TEZ/IVA treatment were pooled with the PEx events in participants in study 661-110 in the PEx Analysis Sets.

In the 106/110 Efficacy Set (*F/F*), endpoints were assessed in two groups who transitioned to study 661-110: participants randomized to PBO (PBO-TEZ/IVA) and those randomized to TEZ/IVA (TEZ/IVA-TEZ/IVA) in study 661-106 (*F/F*). In the 108/110 Efficacy Set (*F*/RF), endpoints were assessed in three groups who transitioned to study 661-110 based on the treatment assignment from period 2 in the parent study: participants randomized to PBO (PBO-TEZ/IVA), IVA (IVA-TEZ/IVA), and TEZ/IVA (TEZ/IVA-TEZ/IVA) in study 661-108 (*F*/RF). In the 106/110 Efficacy Set (*F/F*), for participants who were randomized to the PBO group in study 661-106 (*F/F*), baseline was defined as the most recent nonmissing measurement before the first dose of study drug in study 661-110 because the study specified that a previous value that is available (e.g., Screening) should be used if the Day 1 value was missing. For efficacy analyses of endpoints in all other groups, baseline was defined as the most recent nonmissing measurement before the first dose of study drug in the parent study. Results were not compared between groups within study 661-110; data from groups in study 661-110 and data from parent studies are displayed only to allow visual comparisons.

In the post hoc analysis of rate of lung function decline, TEZ/IVA–treated *F*/*F* participants were matched with up to five eligible *F*/*F* historical controls in the CFFPR using the propensity score method (**appendix pp 12-13**) previously described in similar analyses with IVA and LUM/IVA.[18,19] In this analysis, Global Lung (Function) Initiative (GLI) equations were used to calculate $ppFEV_1$ to be consistent with the CFFPR.[27] W-H equations were used in a sensitivity analysis. For TEZ/IVA–treated participants, the analysis excluded spirometry measurements in the first 22 days after TEZ/IVA initiation in order to exclude acute lung function improvements

observed with TEZ/IVA initiation from the slope estimation. In a sensitivity analysis, to evaluate potential selection bias in comparing a clinical trial population with a registry population, pwCF in the registry who had a record of participating in any clinical trial were excluded from the analysis. Further details about analysis methods, including additional sensitivity analyses, are provided in the **appendix (pp 7-8)**.

SAS version 9.4 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Ethical Considerations

The study protocol was reviewed and approved by local institutional review boards or ethics committees. Written informed consent (and assent, if applicable) was provided before screening. This study was conducted in accordance with the Declaration of Helsinki, local applicable laws and regulations, and current Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Role of the Funding Source

The funder participated in the design of the protocol, conducted the statistical analysis, collected the data, and was involved in the data interpretation. Medical writing, editorial support, and coordination were provided by the funder. All authors had full access to the study data. All authors contributed to data interpretation, conception, drafting, and/or revisions to the manuscript, and all approved the final version that was submitted for publication.

RESULTS

Disposition and Baseline Characteristics of Participants

This study was conducted from August 31, 2015, to May 31, 2019. Of 1044 participants enrolled in study 661-110, 1042 received at least one dose of study drug at any time during the 96-week treatment period of study 661-110 and were included in the Safety Set (**Figure 1**); the Safety Set included participants from all 6 parent studies (study 661-103, n=23; study 661-106, n=462; study 661-107, n=159; study 661-108, n=227; study 661-109, n=138; study 661-111, n=33). Of these 1042 participants, 253 participants (24·3%) who had enrolled in study 661-110 after completing studies 661-107 (*F*/MF) or 661-109 (*F*/gating or *F/R117H*) were discontinued from study 661-110 by the sponsor when these parent studies demonstrated that TEZ/IVA was not efficacious in participants with these mutations versus the study comparator. Participants from the 661-107 (*F*/MF) and 661-109 (*F*/gating or *F/R117H*) studies were included in the Safety Set but not in the Efficacy Sets. Of the 789 remaining participants, 682 (86·4%) completed the 96-week treatment regimen, 24 (3·0%) discontinued due to AEs, and 83 (10·5%) discontinued for other reasons (**appendix p 14**). Among the 24 participants who discontinued TEZ/IVA due to AEs, two participants discontinued TEZ/IVA due to AEs that occurred outside the treatment-emergent period (from start of TEZ/IVA to 28 days after the last dose of TEZ/IVA, as defined in the protocol and statistical analysis plan). Thus, there were 24 discontinuations due to AEs but only 22 discontinuations due to treatment-emergent AEs (TEAEs). There were 741 participants in the FAS, 459 in the 106/110 Efficacy Set (*F/F*), 226 in the 108/110 Efficacy Set (*F*/RF), 479 in the 106/110 PEx Analysis Set (*F/F*), and 233 in the 108/110 PEx Analysis Set (*F*/RF). Demographics and baseline characteristics for the 106/110 (*F/F*) and 108/110 (*F*/RF) Efficacy Sets are reported in **Table 1**. In the 106/110 (*F/F*) and 108/110 (*F*/RF) Efficacy Sets, the mean

(SD) age at screening was 26·1 (10·4) years and 35·1 (14·2) years, respectively, and the mean (SD) baseline ppFEV$_1$ was 60·0 (15·1) and 62·2 (14·5), respectively.

Primary Endpoint: Safety

The mean (SD) TEZ/IVA exposure for participants in the Safety Set was 76·0 (31·8) weeks; after excluding participants from parent studies 661-107 (*F*/MF) and 661-109 (*F*/gating or *F/R117H*) who were discontinued from study 661-110, the mean (SD) exposure was 90·2 (18·2) weeks. Of 1042 participants, 995 (95·5%) had at least one TEAE (**appendix p 15**). The most frequent TEAEs (≥10% of participants) were infective PEx of CF, cough, nasopharyngitis, sputum increased, hemoptysis, headache, pyrexia, oropharyngeal pain, upper respiratory tract infection, abdominal pain, nausea, and diarrhea. Time-adjusted AE rates (number of AEs per 100 participant-years) for the most frequent TEAEs were generally comparable to or lower than the time-adjusted rates for the TEZ/IVA group in study 661-106 (*F/F*) (**Table 2**). The majority of participants had mild or moderate TEAEs that were deemed unlikely related or not related to study drug. Ninety participants (8·6%) had TEAEs leading to treatment interruption, and 22 (2·1%) had TEAEs leading to treatment discontinuation. The most frequent TEAEs leading to treatment discontinuation (occurring in at least two participants) were increased aspartate and alanine aminotransferase (n=4 [0·4%] each), increased blood creatine phosphokinase (n=4 [0·4%]), and infective PEx of CF (n=2 [0·2%]).

Serious TEAEs (SAEs) were experienced by 351 participants (33·7%); the most frequently reported SAEs (occurring in ≥1% of participants) were infective PEx of CF (n=243 [23·3%]), hemoptysis (n=25 [2·4%]), and distal intestinal obstruction syndrome (n=12 [1·2%]). No deaths

occurred during the treatment-emergent period. Two deaths occurred after the treatment-emergent period: one due to influenza-related complications and the other due to esophageal cancer. The investigators deemed the events leading to death as not related to the study drug.

Based on prior experience with CFTR modulators, elevated transaminases and respiratory events and symptoms were predefined as AEs of interest in study 661-110.[28-30] Sixty-four participants (6·1%) had an AE of elevated transaminases, the majority of which were mild or moderate in severity (**appendix p 16**). Five participants (0·5%) had SAEs of elevated transaminases, and five (0·5%) had AEs of elevated transaminases that led to treatment discontinuation. Liver function test results that met threshold criteria are summarized in the **appendix (p 17)**. A total of 181 participants (17·4%) had AEs of respiratory events and symptoms (**appendix p 18**). Most treatment-emergent respiratory events were mild or moderate in severity, and none were serious or led to treatment discontinuation.

No clinically meaningful trends were observed in serum chemistry, hematology, coagulation, urinalysis, vital signs, physical examinations, ophthalmological examinations, standard electrocardiograms, or pulse oximetry.

Secondary Endpoints: Efficacy

In the 106/110 (*F/F*) Efficacy Set, the least squares (LS) mean absolute change from baseline in ppFEV$_1$ at week 96 was 2·1 percentage points (95% CI, 0·8 to 3·3) in the PBO-TEZ/IVA group and 2·0 percentage points (95% CI, 0·7 to 3·2) in the TEZ/IVA-TEZ/IVA group (**appendix pp 19-20**). In the 108/110 (*F*/RF) Efficacy Set, the LS mean absolute change from baseline in

ppFEV$_1$ at week 96 was 4·1 percentage points (95% CI, 2·2 to 6·0) in the PBO-TEZ/IVA group, 6·7 percentage points (95% CI, 4·7 to 8·7) in the IVA-TEZ/IVA group, and 7·5 percentage points (95% CI, 5·6 to 9·4) in the TEZ/IVA-TEZ/IVA group (**appendix pp 21-22**). In the 106/110 (*F/F*) and 108/110 (*F*/RF) Efficacy Sets, PBO-TEZ/IVA participants in study 661-110 had an increase in ppFEV$_1$ that was similar in magnitude to that observed in TEZ/IVA–treated participants in their parent studies. Increases in ppFEV$_1$ observed in each efficacy set in study 661-110 were generally maintained for up to 120 weeks of TEZ/IVA treatment (**appendix pp 19-22; Figure 2A; Figure 3A**). In the 106/110 (*F/F*) and 108/110 (*F*/RF) Efficacy Sets, the increases in relative change in ppFEV$_1$ from baseline (**appendix pp 19-22**) were similar to those for absolute change from baseline in ppFEV$_1$.

In the 106/110 PEx Analysis Set (*F/F*), in the PBO-TEZ/IVA group, the estimated annualized event rates for PEx, PEx requiring intravenous (IV) antibiotics, and PEx requiring hospitalization were 0·68 (95% CI, 0·55 to 0·83), 0·34 (95% CI, 0·25 to 0·44), and 0·23 (95% CI, 0·16 to 0·32), respectively (**appendix pp 19-20**). In the TEZ/IVA-TEZ/IVA group, the estimated annualized event rates for PEx, PEx requiring IV antibiotics, and PEx requiring hospitalization were 0·76 (95% CI, 0·63 to 0·92), 0·36 (95% CI, 0·28 to 0·47), and 0·24 (95% CI, 0·18 to 0·32), respectively.

In the 108/110 PEx Analysis Set (*F*/RF), in the PBO-TEZ/IVA group, the estimated annualized event rates for PEx, PEx requiring IV antibiotics, and PEx requiring hospitalization were 0·44 (95% CI, 0·29 to 0·66), 0·09 (95% CI, 0·04 to 0·22), and 0·07 (95% CI, 0·03 to 0·18), respectively (**appendix pp 21-22**). In the IVA-TEZ/IVA group, the estimated annualized event

394 rates for PEx, PEx requiring IV antibiotics, and PEx requiring hospitalization were 0·28 (95%
395 CI, 0·18 to 0·44), 0·09 (95% CI, 0·04 to 0·22), and 0·09 (95% CI, 0·04 to 0·22), respectively. In
396 the TEZ/IVA-TEZ/IVA group, the estimated annualized event rates for PEx, PEx requiring IV
397 antibiotics, and PEx requiring hospitalization were 0·22 (95% CI, 0·14 to 0·35), 0·05 (95% CI,
398 0·02 to 0·13), and 0·05 (95% CI, 0·02 to 0·13), respectively.
399
400 In the 106/110 (*F/F*) and 108/110 (*F*/RF) PEx Analysis Sets, the estimated PEx event rate per
401 year with TEZ/IVA treatment in study 661-110 was numerically lower than that in the PBO
402 group in the respective 661-106 (*F/F*) and 661-108 (*F*/RF) parent studies and comparable to that
403 in the TEZ/IVA group in these parent studies (**appendix pp 19-22; Figure 2B; Figure 3B**).
404 Improvements in rates of PEx requiring hospitalization and/or IV antibiotics followed a similar
405 pattern as the overall PEx rate in the 106/110 PEx Analysis Set (*F/F*). Rates of PEx requiring
406 hospitalization and rates of PEx requiring treatment with IV antibiotics were not evaluated in
407 study 661-108 (*F*/RF) (due to the short treatment period) but were low in all three groups that
408 transitioned from study 661-108 (*F*/RF) to study 661-110. Time to first PEx is shown in the
409 **appendix (p 24)**, and the event-free probabilities are shown in the **appendix (pp 19-22)**.
410
411 In the 106/110 (*F/F*) Efficacy Set, the LS mean absolute change from baseline in CFQ-R
412 respiratory domain score at week 96 was 1·7 (95% CI, −0·6 to 4·0) in the PBO-TEZ/IVA group
413 and 3·0 (95% CI, 0·7 to 5·3) in the TEZ/IVA-TEZ/IVA group (**appendix pp 19-20**). In the
414 108/110 (*F*/RF) Efficacy Set, the LS mean absolute change from baseline in CFQ-R respiratory
415 domain score at week 96 was 10·3 (95% CI, 7·0 to 13·6) in the PBO-TEZ/IVA group, 11·2
416 (95% CI, 7·7 to 14·7) in the IVA-TEZ/IVA group, and 13·8 (95% CI, 10·3 to 17·2) in the

TEZ/IVA-TEZ/IVA group (**appendix pp 21-22**). In the 106/110 (*F/F*) and 108/110 (*F*/RF) Efficacy Sets, PBO-TEZ/IVA participants in study 661-110 had an improvement in CFQ-R respiratory domain score that was similar in magnitude to the improvement in CFQ-R respiratory domain score observed in TEZ/IVA–treated participants in their parent studies. The benefits in CFQ-R respiratory domain score observed in each efficacy set in study 661-110 were generally maintained for up to 120 weeks of treatment (**appendix pp 19-22; Figure 2C; Figure 3C**).

In the 106/110 (*F/F*) and 108/110 (*F*/RF) Efficacy Sets, increases in BMI and weight observed in the parent studies were generally maintained in all treatment groups over 96 weeks in study 661-110 (**appendix pp 19-22; Figure 2D; Figure 3D**). The mean *z* scores (BMI, weight, and height in participants <20 years of age) remained stable and close to the mean values for the age-matched general population during the 96 weeks in both efficacy sets (**appendix pp 19-22**).

Secondary Endpoint: Pharmacokinetics

The pharmacokinetics exposures to TEZ, IVA, and major metabolites were similar to those observed in the parent studies (data not shown).

Analysis of Rate of Lung Function Decline

A total of 407 *F*/*F* participants receiving TEZ/IVA in study 661-106 (*F/F*) and/or study 661-110 were propensity score–matched to 1383 CFTRm-untreated *F*/*F* historical controls in the CFFPR who met the inclusion criteria (on average, 3·4 controls per TEZ/IVA–treated participant) (**appendix p 25**). The two groups were well matched across baseline characteristics based on effect size differences of <0·20 and *P*>0·10 (**appendix pp 12-13**); in both groups, mean age was

approximately 26 years, and baseline ppFEV$_1$ was approximately 59 (**Table 3**). The time frame for this analysis was 2015 to 2019 for the *F/F* participants receiving TEZ/IVA and 2012 to 2014 for the historical controls. The annualized rate of ppFEV$_1$ decline was significantly lower for TEZ/IVA–treated participants versus untreated matched-control participants: −0·80 (95% CI, −1·31 to −0·30) in the TEZ/IVA group and −2·08 (95% CI, −2·34 to −1·82) in the CFFPR historical control group (**Figure 4**). The mean difference (CFFPR control group versus TEZ/IVA group) was −1·27 per year (95% CI, −1·84 to −0·71; P<0·001), which represents a 61·5% relative reduction (95% CI, 35·8 to 86·1) in the annualized rate of decline in ppFEV$_1$. In the sensitivity analysis excluding registry historical controls who had a record of participating in clinical trials, the resulting difference in the annualized rate of lung function decline was −1·39 per year (95% CI, −1·96 to −0·82; P<0·001), representing a 61·7% relative reduction (95% CI, 38·0 to 84·2) (**appendix p 23**). Additional sensitivity analyses were conducted and yielded consistent findings, with a range of relative reduction from 59·7% to 61·7%.

DISCUSSION

This study is the first to evaluate the long-term safety and efficacy of the dual CFTRm TEZ/IVA. TEZ/IVA was found to be generally safe and well tolerated for up to 96 weeks in this open-label extension study 661-110. With extended treatment in study 661-110, the AE profile of TEZ/IVA remained consistent with prior PBO-controlled parent studies.[20,21] Most pwCF had at least one TEAE over 96 weeks in study 661-110; this finding is not surprising given the morbidity associated with CF and is entirely consistent with prior experience in long-term extension studies of other CFTR modulators.[19,31] No increases in time-adjusted rates of TEAEs were observed following up to 120 weeks of TEZ/IVA treatment, and the rate of discontinuations due to AEs

was low in study 661-110. The most common AEs were generally infectious, respiratory, or gastrointestinal in nature and consistent with the manifestations of CF. In general, time-adjusted rates of AEs were lower in participants in study 661-110 than in TEZ/IVA-treated participants in feeder study 661-106 (*F/F*). This is a typical finding in other 96 week open-label extension studies of other CFTR modulators.[19] One possible explanation for this finding is that recurrent AEs are less frequently captured over longer-term treatment. PwCF experience elevations in transaminase levels due to underlying hepatic disease and treatment with concomitant medications, including antibiotics[32-34]; the transaminase data in study 661-110 were generally consistent with previous experience with TEZ/IVA and background transaminase elevations occurring in pwCF.[20,21] Consistent with the PBO-controlled parent studies, there was no evidence of an increased incidence of respiratory TEAEs associated with extended TEZ/IVA treatment.[20,21]

CF is a severe progressive disease, and maintaining or improving lung function is an important goal in the management of pwCF because loss of lung function is the major driver of increased morbidity and mortality.[5] TEZ/IVA use was associated with two important effects on CF lung disease. First, participants with *F/F* and *F/*RF genotypes experienced an acute improvement in lung function, which was observed by day 15 following initiation of TEZ/IVA in both the parent studies and study 661-110 (for those who received PBO in the parent studies). Improvements in ppFEV$_1$ observed in TEZ/IVA-treated participants with the *F/F* and *F/*RF genotypes were generally maintained in study 661-110. Second, a 61·5% relative reduction in the rate of lung function decline was demonstrated in participants with the *F/F* genotype compared with a cohort of CFTRm-untreated historical controls from the CFFPR. Study 661-110 was not designed to

compare the magnitude of the effect of TEZ/IVA with that of other CFTRm on clinical outcome assessments. However, these results are consistent with prior published studies showing that CFTR modulation with IVA and LUM/IVA significantly reduced the long-term rate of lung function decline in participants with the *G551D* mutation by 47·1% (data not shown) and with the *F/F* genotype by 42%, respectively.[18,19] It was not possible to examine the effect of TEZ/IVA on the rate of lung function decline in participants with *F/*RF genotypes due to the limited sample size of eligible participants in the registry. However, it is noteworthy that the benefits in lung function observed in participants with *F*/RF genotypes were generally maintained for up to 104 weeks of treatment.

PEx are important events in the lives of pwCF and have been independently associated with progressive lung function decline and an increased risk of mortality.[35-37] The reductions in the risk of PEx observed with TEZ/IVA treatment in studies 661-106 (*F/F*) and 661-108 (*F*/RF) were generally maintained for up to 120 weeks of treatment in study 661-110, with an annualized PEx rate similar to that observed in the parent studies. The reduction in the PEx rate with extended TEZ/IVA treatment may have contributed to the slower rate of lung function decline in *F/F* participants. Improvements in CFQ-R respiratory domain scores were generally maintained in *F/F* and *F/*RF participants, indicating that TEZ/IVA reduced the respiratory symptom burden during long-term treatment. Improving growth and nutritional parameters is an important goal in the management of pwCF because they are important determinants of lung function and survival in pwCF.[38,39] Improvements in BMI that were observed in the parent studies were generally maintained in study 661-110. In participants <20 years of age in study 661-110, growth

parameters were maintained close to those for the age-matched general population without CF (as assessed by *z* scores).

The clinical benefit observed in study 661-110 was consistent with that observed in the parent studies. Although study 661-110 was not a PBO-controlled study and lacked a long-term comparator group, the results are interpretable because pwCF with *F/F* and *F*/RF genotypes who are not treated with CFTRm have multisystem disease that progresses over time, including relentless loss of lung function.[4,7] The analysis of rate of lung function decline, which demonstrated that TEZ/IVA was associated with slower lung function decline versus matched historical controls not treated with CFTRm, was a post hoc analysis, and causality cannot be definitively established. The analysis used a cohort of historical controls from the US CFFPR between 2012 and 2014 to avoid the confounding effect of use of LUM/IVA in the *F/F* population because this CFTRm was approved by the US Food and Drug Administration for this population in 2015; the time frame for the *F/F* participants receiving TEZ/IVA in this study was 2015 to 2019. The use of a noncontemporaneous cohort has the potential to introduce a temporal bias due to possible secular changes in lung function decline due to changes in clinical care. However, to our knowledge, no major advances in background CF care management occurred during this time. Nevertheless, because this analysis employed rigorous epidemiological and statistical methods, including propensity score matching, to balance the risk factors of lung function decline between groups, any bias introduced due to the use of noncontemporaneous controls would likely be addressed. Although the ability to match participants was limited to the variables collected in both the registry and the clinical study, the analysis accounted for the most important variables that are known to influence lung function decline based on the published

literature. In evaluating a sensitivity analysis of the potential for selection bias in comparing a clinical trial population with a registry population, we observed consistent results indicating that no such bias exists in our analysis. The registry included data from participants in the United States, whereas study 661-110 enrolled participants not only in the United States but also in Canada, Europe, and Australia, where the characteristics of the pwCF may differ. It is not possible, due to sample size limitations, to restrict the rate of decline in FEV_1 analysis to one geographical region. Other limitations of this analysis are that the model that estimated the mean annual rate of decline was based on $ppFEV_1$ measurements from variable observation periods across participants included in the analysis. Also, the model assumed that the rate of decline in $ppFEV_1$ was constant over the observation period for each participant.

A limitation of this study is its open-label design, which may be associated with potential biases including biases in symptom reporting by study participants, evaluation of the severity and relatedness of AEs to study drug by site investigators, and patient-reported outcomes, including the CFQ-R respiratory domain score. Other limitations of our efficacy assessments include the fact that participants with *F*/RF genotypes were evaluated as a group due to the rare prevalence of these RF mutations. Due to small sample sizes, it is not possible to provide efficacy data for TEZ/IVA on individual *F*/RF genotypes. However, the results indicate that TEZ/IVA treatment led to improvements in efficacy endpoints over the longer term in pwCF with *F*/RF genotypes who were included in study 661-110.

TEZ/IVA is the foundation of a triple-combination CFTRm therapy (elexacaftor [ELX]/TEZ/IVA). A recent Phase 3 study confirmed that ELX/TEZ/IVA resulted in significant

554 and clinically meaningful improvements in ppFEV$_1$, sweat chloride concentrations, and CFQ-R
555 respiratory domain scores, and clinical meaningful improvements in nutritional parameters
556 compared with TEZ/IVA dual-combination therapy in participants ≥12 years of age with CF
557 with the *F/F* genotype.[40] ELX/TEZ/IVA combination therapy was recently approved in the
558 United States to treat pwCF ≥12 years of age with at least one copy of the *F508del-CFTR*
559 mutation,[41] noting that its effect on long-term lung function decline has not yet been reported.
560
561 Study 661-110 showed that TEZ/IVA was generally safe and well tolerated for up to 120 weeks
562 and had a safety profile consistent with that observed in the parent studies. The multisystem
563 clinical benefits observed with TEZ/IVA in the parent studies in participants with *F/F* and *F*/RF
564 genotypes were generally maintained over 96 weeks and were also observed in participants who
565 transitioned from PBO to TEZ/IVA in study 661-110. The post hoc analysis of rate of lung
566 function decline demonstrated that TEZ/IVA was associated with a significantly slower lung
567 function decline among *F/F* participants vs CFTRm-untreated matched historical controls. Thus,
568 longer-term TEZ/IVA use was associated with sustained benefits, and the rate of lung function
569 decline was significantly reduced in *F*/*F* participants consistent with modification of the course
570 of CF disease. These results support the clinical benefit of long-term TEZ/IVA treatment for *F/F*
571 or *F*/RF pwCF ≥12 years of age.
572

CONTRIBUTORS

All authors contributed to data interpretation, conception, drafting, and/or revisions to the manuscript, and all approved the final version that was submitted for publication. **CAO:** study design, data collection, data analysis, and literature searches. **CB:** no additional contributions. **CEW:** data collection. **DC:** data analysis. **DGD:** data collection. **DJP:** statistical analysis and interpretation of analysis. **GSS:** study design. **HPD:** no additional contributions. **JLR:** study design, analysis, and interpretation of the rate of lung function decline and development of the manuscript. **KDB:** conceptualization and design of the report and figure layout. **MJ:** no additional contributions. **NA:** data collection and data analysis. **PAF:** study design, data collection, and data analysis. **PC:** data analysis. **RF:** data collection. **RFB:** data analysis. **SJM:** analysis design and statistical analysis. **XH:** study design, data interpretation, and writing the manuscript, all with a focus on the analysis of the rate of lung function decline. **XW:** data analysis and figures. **YY:** study design, analysis, and interpretation of the rate of lung function decline and development of the manuscript.

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DATA SHARING STATEMENT

Vertex is committed to advancing medical science and improving the health of people with cystic fibrosis. 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.

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REFERENCES

1 De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. *Lancet Respir Med* 2016; **4**: 662–74.

2 Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989; **245**: 1066–73.

3 Dalemans W, Barbry P, Champigny G, et al. Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. *Nature* 1991; **354**: 526–8.

4 Salvatore D, Padoan R, Buzzetti R, et al. Patients with cystic fibrosis having a residual function mutation: data from the Italian registry. *Pediatr Pulmonol* 2019; **54**: 150–7.

5 Elborn JS. Cystic fibrosis. *Lancet* 2016; **388**: 2519–31.

6 Castellani C, Cuppens H, Macek M Jr, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. *J Cyst Fibros* 2008; **7**: 179–96.

7 McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. *Chest* 2006; **130**: 1441–7.

8 Cystic Fibrosis Foundation. The clinical and functional translation of CFTR (CFTR2). https://www.cftr2.org/. Accessed September 16, 2020.

9 McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet* 2003; **361**: 1671–6.

10 Comer DM, Ennis M, McDowell C, et al. Clinical phenotype of cystic fibrosis patients with the G551D mutation. *QJM* 2009; **102**: 793–8.

11 Rodman DM, Polis JM, Heltshe SL, et al. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. *Am J Respir Crit Care Med* 2005; **171**: 621–6.

12 Van Goor F, Hadida S, Grootenhuis PD, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A* 2009; **106**: 18825–30.

13 Van Goor F, Grootenhuis P, Hadida S, et al. Nonclinical profile of the CFTR corrector VX-661. *Pediatr Pulmonol* 2016; **51** [abstract 217].

14 Van Goor F, Hadida S, Grootenhuis PDJ, et al. Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. *Proc Natl Acad Sci U S A* 2011; **108**: 18843–8.

15 Keating D, Marigowda G, Burr L, et al. VX-445–tezacaftor–ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. *N Engl J Med* 2018; **379**: 1612–20.

16 Bessonova L, Volkova N, Higgins M, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018; **73**: 731–40.

17 Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. *J Cyst Fibros* 2020; **19**: 68–79.

18 Sawicki GS, McKone EF, Pasta DJ, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med* 2015; **192**: 836–42.

19 Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017; **5**: 107–18.

20 Taylor-Cousar J, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med* 2017; **377**: 2013–23.

21 Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med* 2017; **377**: 2024–35.

22 Symdeko (tezacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Inc; 2019.

23 Symkevi (tezacaftor/ivacaftor) [summary of product characteristics]. Dublin, Ireland: Vertex Pharmaceuticals (Ireland) Ltd; 2019.

24 Munck A, Kerem E, Ellemunter H, et al. Tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for minimal function CFTR mutations. *J Cyst Fibros* 2020 June 13 [Epub ahead of print].

25 Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993; **15**: 75–88.

26 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; **159**: 179–87.

27 Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**: 1324–43.

28 Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015; **373**: 220–31.

29 Elborn JS, Ramsey BW, Boyle MP, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *Lancet Respir Med* 2016; **4**: 617–26.

30 Kalydeco (ivacaftor) [package insert]. Boston, MA, United States: Vertex Pharmaceuticals Inc; 2019.

31 McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). *Lancet Respir Med* 2014; **2**: 902–10.

32 Ledder O, Haller W, Couper RT, Lewindon P, Oliver M. Cystic fibrosis: an update for clinicians. Part 2: hepatobiliary and pancreatic manifestations. *J Gastroenterol Hepatol* 2014; **29**: 1954–62.

33 Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. *J Antimicrob Chemother* 2011; **66**: 1431–46.

34 Jong T, Geake J, Yerkovich S, Bell SC. Idiosyncratic reactions are the most common cause of abnormal liver function tests in patients with cystic fibrosis. *Intern Med J* 2015; **45**: 395–401.

35 Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J* 2012; **40**: 61–6.

36 de Boer K, Vandemheen KL, Tullis E, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. *Thorax* 2011; **66**: 680–5.

37 Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* 2007; **151**: 134–9.e1.

38 Konstan MW, Butler SM, Wohl MEB, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr* 2003; **142**: 624–30.

39 Sharma R, Florea VG, Bolger AP, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. *Thorax* 2001; **56**: 746–50.

40 Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019; **394**: 1940–8.

41 Vertex Pharmaceuticals Incorporated. FDA approves TRIKAFTA (elexacaftor/tezacaftor/ivacaftor and ivacaftor) to treat the underlying cause of cystic fibrosis in people ages 12 and older who have at least one F508del mutation [press release]. 2019.

42 Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. *Pharmacoepidemiol Drug Saf* 2008; **17**: 1218–25.

738 **TABLES**

739 **Table 1. Participant Demographics and Baseline Characteristics**

	106/110 Efficacy Set (*F/F*) (n=459)	**108/110 Efficacy Set (*F*/RF) (n=226)**
Age at screening, mean (SD), years	26·1 (10·4)	35·1 (14·2)
Age ≥18 years at screening, n (%)	350 (76·3)	194 (85·8)
Female sex, n (%)	222 (48·4)	121 (53·5)
White race, n (%)	454 (98·9)	221 (97·8)
BMI, mean (SD), kg/m^2	21·00 (2·94)	24·21 (5·00)
$ppFEV_1$, mean (SD)	60·0 (15·1)	62·2 (14·5)
$ppFEV_1$ category, n (%)		
<40%	42 (9·2)	20 (8·8)
≥40% to <70%	283 (61·7)	132 (58·4)
≥70% to ≤90%	125 (27·2)	70 (31·0)
>90%	8 (1·7)	4 (1·8)

740 BMI, body mass index; $ppFEV_1$, percent predicted forced expiratory volume in 1 second using

741 Wang and Hankinson equations.

742

Table 2. Time-Adjusted TEAEs in ≥10% of Participants in the Study 661-106 (*F/F*) Safety Set's TEZ/IVA Group or in the Study 661-110 (*F/F* and *F*/RF) Safety Set

	Study 661-106 (*F/F*) Safety Set[a] (n=509)				Study 661-110 (*F/F* and *F*/RF) Safety Set (n=1042)	
	PBO (n=258)		TEZ/IVA (n=251)		TEZ/IVA (n=1042)	
	Participants, n (%)	Events Per 100 Participant-Years[b]	Participants, n (%)	Events Per 100 Participant-Years[b]	Participants, n (%)	Events Per 100 Participant-Years[b]
Any TEAE	245 (95·0)	1344·78	227 (90·4)	1086·15	995 (95·5)	661·47
Infective PEx of CF	96 (37·2)	126·02	75 (29·9)	92·25	549 (52·7)	91·11
Cough	84 (32·6)	101·34	66 (26·3)	75·97	374 (35·9)	46·31
Nasopharyngitis	39 (15·1)	48·47	42 (16·7)	48·84	227 (21·8)	24·18
Hemoptysis	35 (13·6)	41·42	26 (10·4)	30·75	179 (17·2)	23·72
Sputum increased	42 (16·3)	42·30	36 (14·3)	37·08	224 (21·5)	21·28
Headache	37 (14·3)	52·87	44 (17·5)	51·55	147 (14·1)	19·83
Pyrexia	32 (12·4)	33·49	28 (11·2)	35·27	136 (13·1)	14·16
Oropharyngeal pain	29 (11·2)	31·72	22 (8·8)	20·80	136 (13·1)	12·52
Upper respiratory tract infection	10 (3·9)	10·57	7 (2·8)	8·14	135 (13·0)	11·86
Abdominal pain	22 (8·5)	25·56	23 (9·2)	25·32	107 (10·3)	9·35
Nausea	18 (7·0)	18·51	23 (9·2)	23·51	107 (10·3)	9·29
Diarrhea	23 (8·9)	28·20	17 (6·8)	18·99	105 (10·1)	8·30

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; *F/F*, homozygous for the *F508del-CFTR* mutation; *F*/RF, heterozygous for the *F508del-CFTR* mutation and a residual function *CFTR* mutation; PBO, placebo; PEx, pulmonary exacerbation; TEAE, treatment-emergent adverse event; TEZ/IVA, tezacaftor/ivacaftor combination therapy.

[a] The study 661-106 (*F/F*) Safety Set included all participants who received at least one dose of the study drug in study 661-106 (*F/F*).

749 [b] The number of events per 100 participant-years equaled the number of events/(total exposure in days/[365·25 × 100]).

Table 3. Demographics and Baseline Characteristics of *F/F* Participants Included in the Post Hoc Analysis of Rate of $ppFEV_1$ Decline

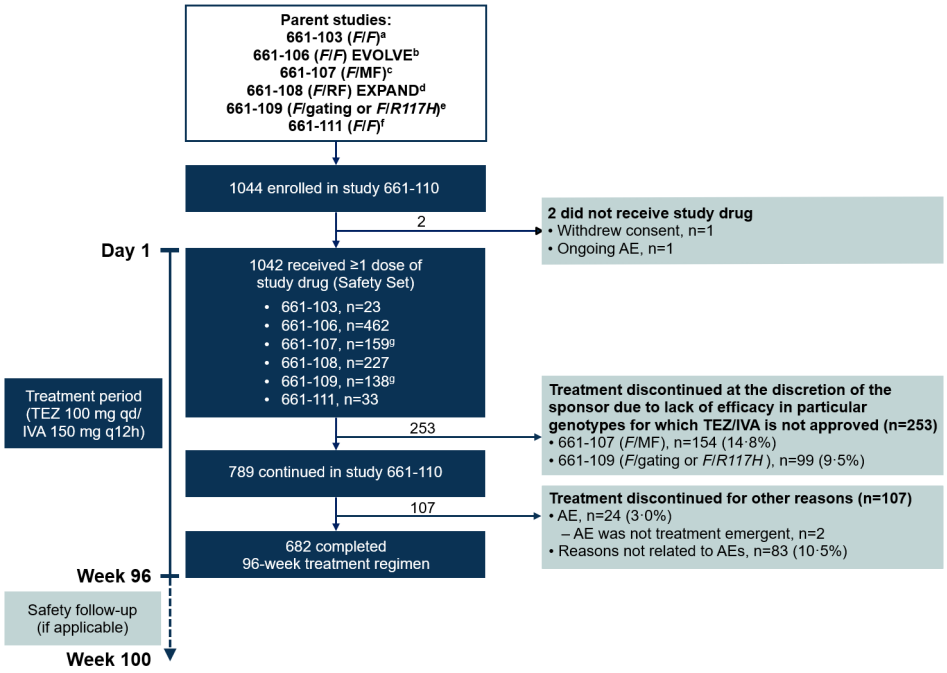
	TEZ/IVA–Treated Group (n=407)	CFFPR Matched-Control Group[a] (n_w=407; n=1383)
Age at baseline, mean (SD), years	26·03 (10·35)	26·04 (5·57)
≥18 years of age at baseline, n (%)	310 (76·2)	310 (76·2)
Female sex, n (%)	191 (46·9)	182 (44·7)
CF-related diabetes prior to baseline, n (%)	72 (17·7)	75 (18·4)
BMI, mean (SD), kg/m^2	21·03 (2·97)	21·13 (1·66)
$ppFEV_1$, mean (SD)	58·95 (14·54)	59·43 (9·25)
Pseudomonas positive, n (%)	292 (71·7)	286 (70·4)
Dornase alfa, n (%)	293 (72·0)	307 (75·4)
Inhaled corticosteroid, n (%)	152 (37·3)	131 (32·1)

BMI, body mass index; CF, cystic fibrosis; CFFPR, CF Foundation Patient Registry; CFTR, CF transmembrane conductance regulator; *F/F*, homozygous for the *F508del-CFTR* mutation; GLI, Global Lung (Function) Initiative; $ppFEV_1$, percent predicted forced expiratory volume in 1 second using GLI equations; TEZ/IVA, tezacaftor/ivacaftor combination therapy.

[a] n_w represents the weighted sample size of the historical control group using the inverse of the number of controls in each matched set to account for one-to-many matching used in the analysis.[42]

FIGURES

Figure 1. Study Design



AE, adverse event; CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; IVA, ivacaftor; *F/F*, homozygous for the *F508del-CFTR* mutation; *F*/gating, heterozygous for the *F508del-CFTR* mutation and a *CFTR* gating mutation; *F/*MF, heterozygous for the *F508del-CFTR* mutation and a minimal function *CFTR* mutation; *F/R117H*, heterozygous for the *F508del-CFTR* mutation and the *R117H-CFTR* mutation; *F*/RF, heterozygous for the *F508del-CFTR* mutation and a residual function *CFTR* mutation; PBO, placebo; qd, once daily; q12h, once every 12 hours; TEZ, tezacaftor; TEZ/IVA, tezacaftor/ivacaftor.

[a] Study 661-103 was a Phase 2, randomized, PBO-controlled, 12-week study of TEZ/IVA in participants ≥18 years of age with CF with the *F/F* genotype.

[b] Study 661-106 was a Phase 3, randomized, PBO-controlled, 24-week study of TEZ/IVA in participants ≥12 years of age with CF with the *F/F* genotype.[20]

[c] Study 661-107 was a Phase 3, randomized, PBO-controlled, 12-week study of TEZ/IVA in participants ≥12 years of age with CF with an *F*/MF genotype.[24]

[d] Study 661-108 was a Phase 3, randomized, PBO- and IVA-controlled, crossover study of TEZ/IVA (2 8-week interventional periods) in participants ≥12 years of age with CF with an *F*/RF genotype.[21]

[e] Study 661-109 was a Phase 3, randomized, IVA-controlled, 8-week study of TEZ/IVA in participants ≥12 years of age with CF with an *F*/gating or *F/R117H* genotype.

[f] Study 661-111 was a Phase 2, randomized, PBO-controlled, 29-day study of TEZ/IVA in participants ≥18 years of age with CF with the *F/F* genotype.

[g] Participants who had enrolled in study 661-110 after completing study 661-107 (*F*/MF) or 661-109 (*F*/gating or *F/R117H*) were discontinued from study 661-110 by the sponsor when the parent study demonstrated that TEZ/IVA was not efficacious in these participants versus the study comparator.

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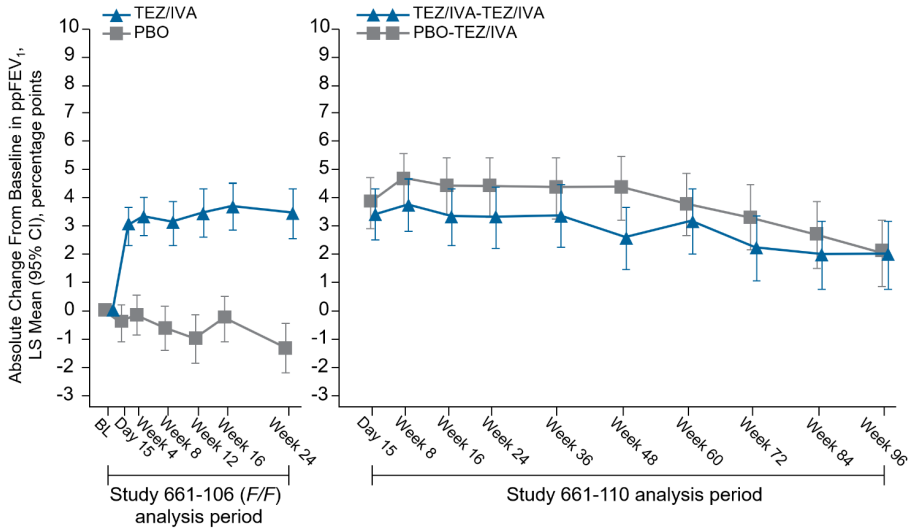
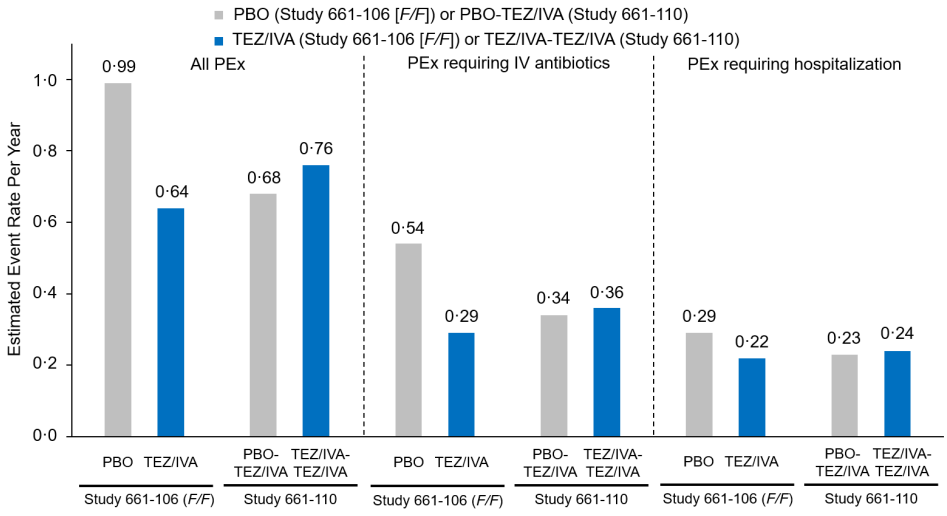
Figure 2. 106/110 Efficacy Results (*F/F*)

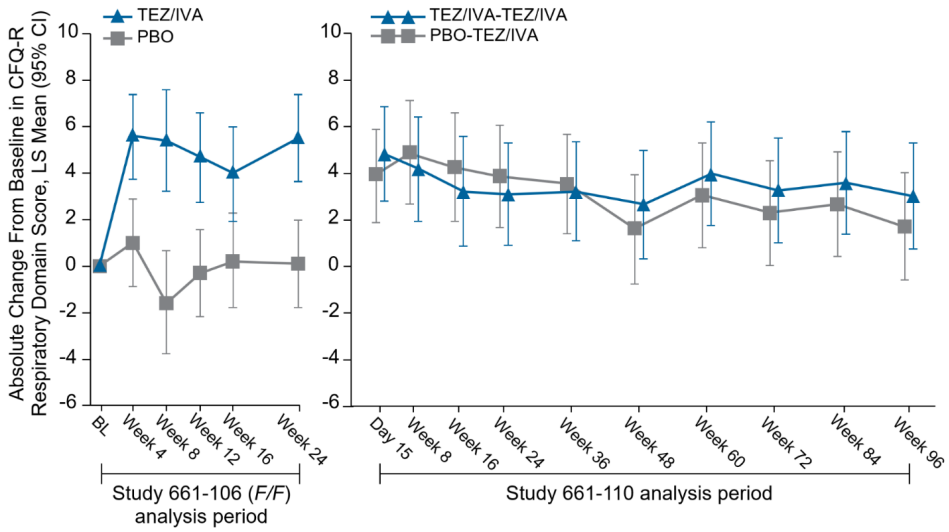
A. Absolute Change From Baseline in $ppFEV_1$[a]



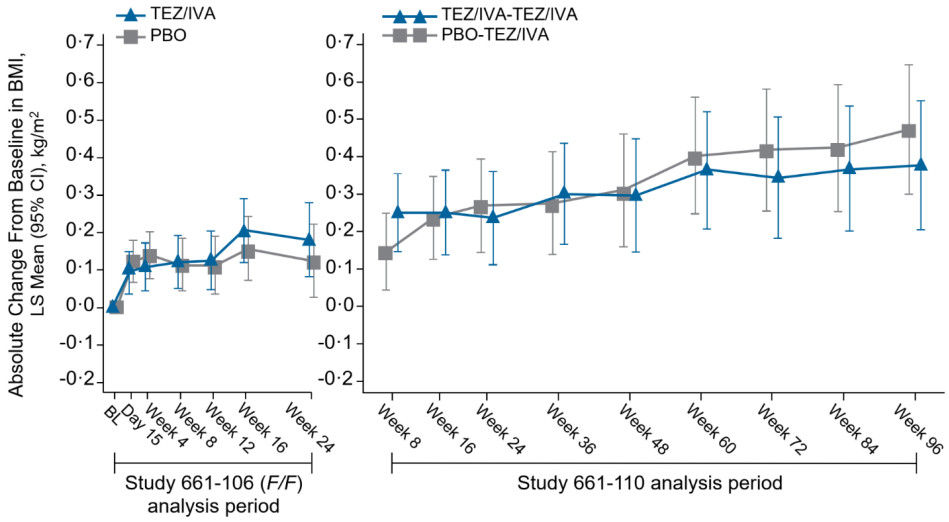
B. PEx Rates in Study 661-106 (*F/F*) and Study 661-110[b,c]



C. Absolute Change From Baseline in CFQ-R Respiratory Domain Score[a]



D. Absolute Change From Baseline in BMI[a]



BL, baseline; BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CFTR, cystic fibrosis transmembrane conductance regulator; *F/F*, homozygous for the *F508del-CFTR*

mutation; IV, intravenous; LS, least squares; PBO, placebo; PEx, pulmonary exacerbation; $ppFEV_1$, percent predicted forced expiratory volume in 1 second using Wang and Hankinson equations; TEZ/IVA, tezacaftor/ivacaftor combination therapy.

[a] Analyses were conducted on the 106/110 Efficacy Set (*F/F*). Data from the PBO and TEZ/IVA groups in the 661-106 (*F/F*) parent study are shown only for visual comparison. Statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.

[b] Analysis was conducted on the 106/110 PEx Analysis Set (*F/F*). The PEx event rates in the PBO and TEZ/IVA groups of the 661-106 (*F*/*F*) parent study are shown only for visual comparison. Statistical comparisons were not performed between groups within study 661-110 or between this study and the parent study.

[c] Annualized PEx rate was calculated based on 48 weeks in a year.

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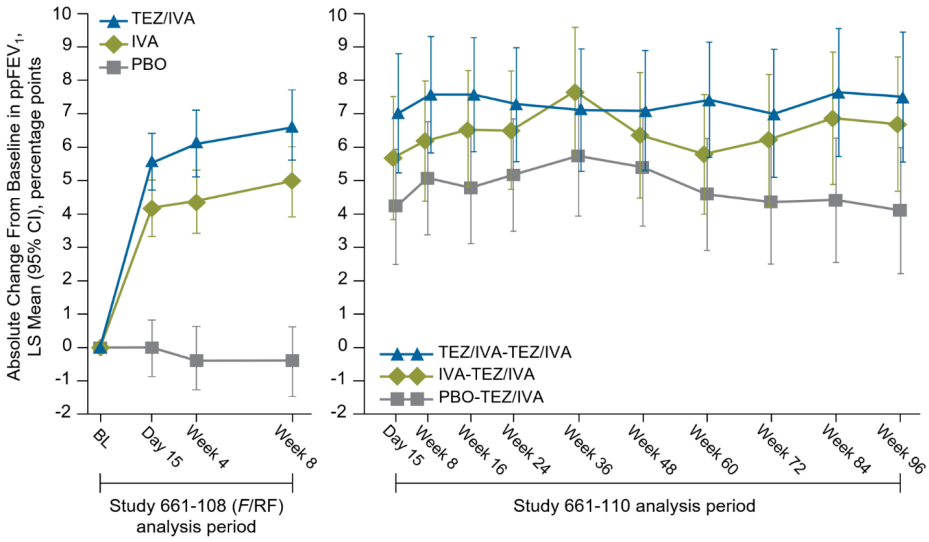
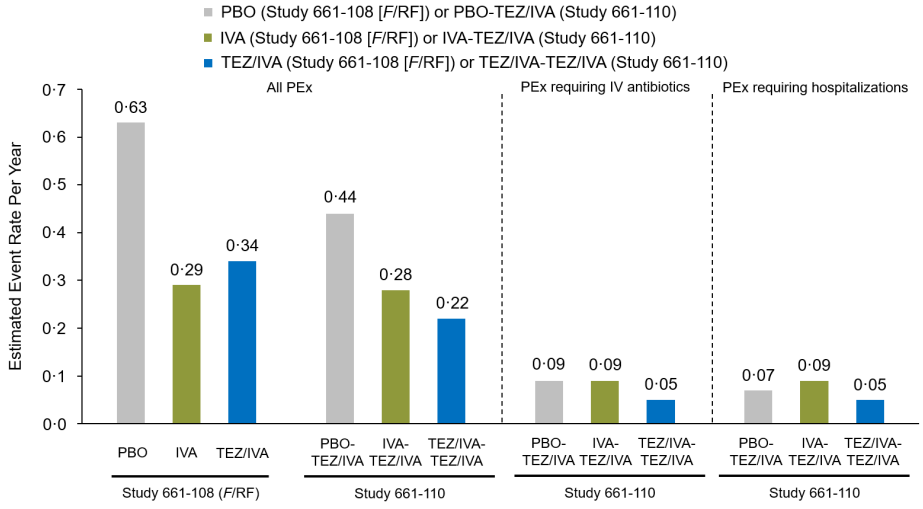
Figure 3. 108/110 Efficacy Results (*F*/RF)

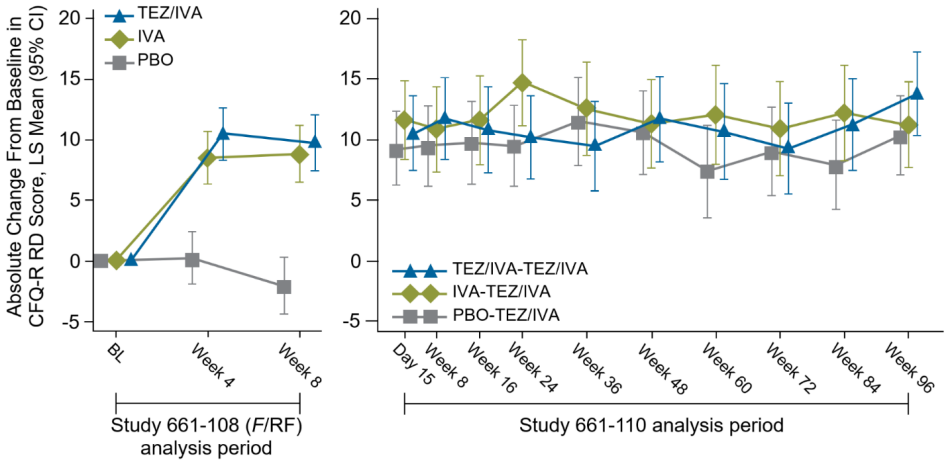
A. Absolute Change From Baseline in ppFEV$_1$[a]



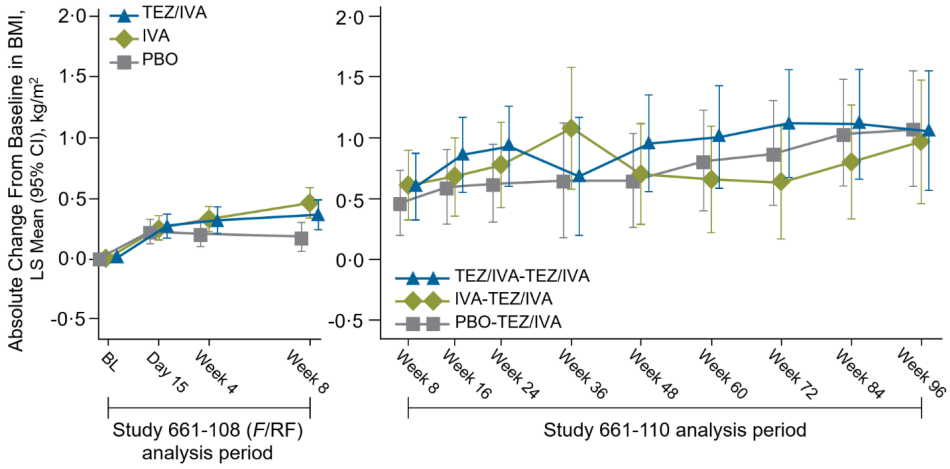
B. PEx Rates in Study 661-108 (*F*/RF) and Study 661-110[b,c]



C. Absolute Change From Baseline in CFQ-R Respiratory Domain Score[a]



D. Absolute Change From Baseline in BMI[a]



BL, baseline; BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CFTR, cystic fibrosis transmembrane conductance regulator; *F*/RF, heterozygous for the *F508del-CFTR* mutation and a residual function *CFTR* mutation; IV, intravenous; IVA, ivacaftor monotherapy; LS, least squares; PBO, placebo; PEx, pulmonary exacerbation; ppFEV$_1$, percent predicted

832 forced expiratory volume in 1 second using Wang and Hankinson equations; TEZ/IVA,
833 tezacaftor/ivacaftor combination therapy.
834 [a] Analyses were conducted on the 108/110 Efficacy Set (*F*/RF). Data from the PBO, IVA, and
835 TEZ/IVA groups in the 661-108 (*F*/RF) parent study are shown only for visual comparison.
836 Statistical comparisons were not performed between groups within study 661-110 or between
837 this study and the parent study.
838 [b] Analysis was conducted on the 108/110 PEx Analysis Set (*F*/RF). The PEx event rates in the
839 PBO, IVA and TEZ/IVA groups of the 661-108 (*F*/RF) parent study are shown only for visual
840 comparison. Statistical comparisons were not performed between groups within study 661-110 or
841 between this study and the parent study.
842 [c] Annualized PEx rate was calculated based on 48 weeks in a year.
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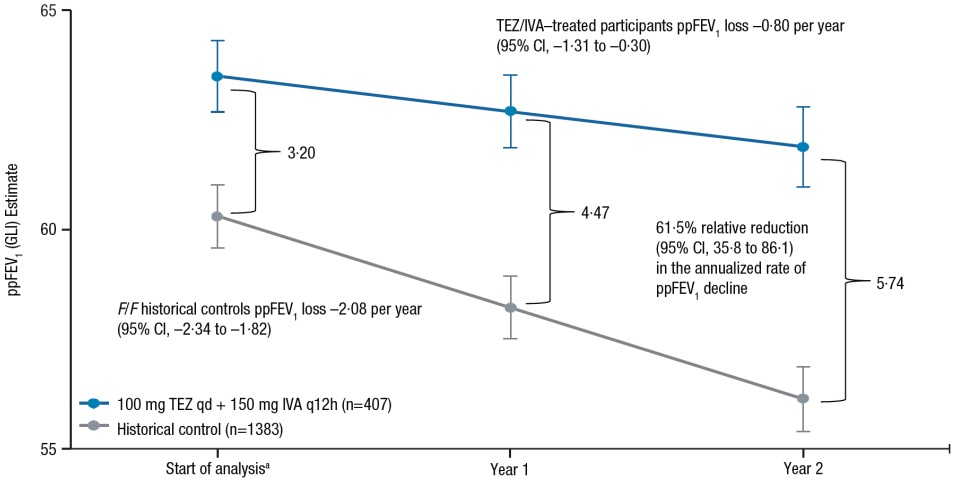
845

Figure 4. Rate of ppFEV$_1$ Decline in Participants With the *F/F* Genotype



CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; *F/F*, homozygous for the *F508del-CFTR* mutation; GLI, Global Lung (Function) Initiative; LUM/IVA, lumacaftor/ivacaftor; ppFEV$_1$, percent predicted forced expiratory volume in 1 second using GLI equations; q12h, once every 12 hours; qd, once daily; TEZ/IVA, tezacaftor/ivacaftor combination therapy. The *F*/*F* historical controls were propensity-matched controls from the Cystic Fibrosis Foundation Patient Registry between 2012 and 2014 to avoid the confounding effect of use of LUM/IVA, a CFTR modulator that was approved by the US Food and Drug Administration for this population in 2015.

[a] Start of analysis was defined as 22 days after TEZ/IVA initiation to remove the acute lung function improvement with TEZ/IVA from the calculation of rate of ppFEV$_1$ decline.

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