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Original Article

Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study

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ABSTRACT

Background: Phase 3 clinical trials showed elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was safe and efficacious in people with cystic fibrosis (CF) with ≥1 *F508del-CFTR* allele. To assess long-term effects of ELX/TEZ/IVA under real-world conditions of use, a 5-year observational registry-based study is being conducted. We report interim results from the first 2 years of follow-up.

Methods: The study included people with CF in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) who initiated ELX/TEZ/IVA between October 2019 and December 2020. Pulmonary exacerbations (PEx), percent predicted forced expiratory volume in 1 second ($ppFEV_1$), hospitalizations, bacterial pathogens, body mass index (BMI), CF complications and comorbidities, and liver function tests (LFTs) after treatment initiation were compared with the 5-year pre-treatment period. Death and lung transplantation were assessed relative to 2019 CFFPR data.

Results: 16,116 people with CF were included (mean treatment duration 20.4 months). Among those with 5 years of pre-treatment data, mean PEx/patient/year declined to 0.18 (95% CI: 0.17, 0.19) in Years 1 and 2 post-treatment from 0.86 (95% CI: 0.83, 0.88) in the baseline year (79% reduction), after a continued increase observed pre-treatment. Similarly, a decline in mean hospitalizations/patient/year was observed in Year 1 that was sustained in Year 2 (74% reduction from baseline year). The mean absolute change in $ppFEV_1$ from baseline was +8.2 percentage points (95% CI: 8.0, 8.4) in Year 1 and +8.9 percentage points (95% CI: 8.7, 9.1) in Year 2, after a continued decline observed pre-treatment. Positive bacterial cultures decreased for all evaluated pathogens, and mean BMI increased by 1.6 kg/m^2 (95% CI: 1.5, 1.6) by Year 2. No new safety concerns were identified based on evaluation of CF complications, comorbidities, and LFTs. The annualized rates of death (0.47% [95% CI: 0.39, 0.55]) and lung transplantation (0.16% [95% CI: 0.12, 0.22]) were considerably lower than reported in 2019 (1.65% and 1.08%, respectively).

Conclusions: ELX/TEZ/IVA treatment was associated with sustained improvements in lung function, reduced frequency of PEx and all-cause hospitalization, increased BMI, and lower prevalence of positive bacterial cultures. Additionally, there was a 72% lower rate of death and 85% lower rate of lung transplantation relative to the year before ELX/TEZ/IVA availability. These results, from the largest cohort of ELX/TEZ/IVA-treated people to date, extend our understanding of the broad clinical benefits of ELX/TEZ/IVA.

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; ELX, elexacaftor; *F/F*, homozygous for *F508del-CFTR*; *F*/G, heterozygous for *F508del-CFTR* and a gating mutation; *F*/MF, heterozygous for *F508del-CFTR* and a minimal function mutation; *F*/RF, heterozygous for *F508del-CFTR* and a residual function mutation; IQR, interquartile range; IVA, ivacaftor; PEx, pulmonary exacerbations; LFT, liver function test; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor.

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1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, leading to reductions in the quantity and/or function of CFTR protein, an anion channel present in various epithelial cells [1–4]. The *F508del-CFTR* mutation is the most common *CFTR* mutation, with nearly 90% of people with CF in some regions of the world having ≥1 *F508del-CFTR* allele [5].

CFTR modulators are small-molecule therapeutics designed to treat the underlying cause of CF, with CFTR potentiators ameliorating the impaired gating associated with some mutant CFTR proteins and CFTR correctors addressing the processing and trafficking defects associated with other mutant CFTR proteins [6,7]. The triple-combination regimen of elexacaftor (ELX) (CFTR corrector), tezacaftor (TEZ) (CFTR corrector), and ivacaftor (IVA) (CFTR potentiator) was shown in pivotal Phase 3 clinical trials to be efficacious and safe in people with CF with ≥1 *F508del-CFTR* allele [8–10]. Treatment with ELX/TEZ/IVA led to robust and clinically meaningful improvements in lung function (as assessed by percent predicted forced expiratory volume in 1 second [$ppFEV_1$]), CFTR function (as assessed by sweat chloride concentration), and respiratory symptoms (as assessed by Cystic Fibrosis Questionnaire-Revised respiratory domain score), exceeding improvements seen with the dual CFTR modulator regimen TEZ/IVA in people with CF homozygous for *F508del-CFTR* [11]. These results demonstrated that ELX/TEZ/IVA is a superior treatment option for people with CF with ≥1 *F508del-CFTR* allele.

In addition to findings from clinical trials and their open-label extensions [12,13], it is important to understand the effects of ELX/TEZ/IVA under real-world conditions of use. Here, we report interim analysis results, including up to 2 years of post-treatment outcome data, from an observational, registry-based, 5-year study designed to assess long-term effects of ELX/TEZ/IVA treatment in people with CF.

2. Methods

2.1. Study objective, design, and population

This 5-year observational registry-based cohort study is being conducted as a post-marketing commitment to the European Medicines Agency. The study is designated as a post-authorization safety study and is disclosed on the European Union electronic Register of Post-Authorization Studies (EUPAS43022). The study objective is to evaluate disease progression and safety outcomes among people with CF treated with ELX/TEZ/IVA. The results from the second of five planned annual interim analyses are reported here.

For this interim analysis, the data source was the US Cystic Fibrosis Foundation Patient Registry (CFFPR). The US CFFPR is the largest national CF disease registry worldwide, collecting data across >120 Cystic Fibrosis Foundation-accredited care centers and representing approximately 84% of all people in the United States with CF [14]. In 2021, 32,100 people with CF were included in the registry [15]. Informed consent/assent is obtained as part of registry enrollment procedures.

The study population included all people with CF, regardless of age or genotype, with a record of ELX/TEZ/IVA initiation in the US CFFPR between October 21, 2019 (date of US Food and Drug Administration approval in the United States) and December 31, 2020. Patients were followed from their date of ELX/TEZ/IVA initiation (considered the index date for all analyses) until death, loss to follow-up, treatment discontinuation (defined as documentation of >90 days with no ELX/TEZ/IVA exposure), or December 31, 2021 (data lock point).

At the request from the European Medicines Agency, evaluations of disease progression and safety outcomes were performed in subsets of the study population with non-missing clinical encounters and non-missing outcome data in the registry for the 5 years before treatment initiation and non-missing outcome data following treatment initiation. The patterns of outcomes during this 5-year pre-treatment period were evaluated to provide additional context to the post-treatment outcome patterns.

2.2. Study outcomes

The CF disease progression/effectiveness outcomes evaluated included: (i) pulmonary exacerbations (PEx), defined as episodes requiring intravenous antibiotic use at home or in the hospital; (ii) hospitalizations due to any reason; (iii) lung function as assessed by $ppFEV_1$ (pulmonary function tests only available among individuals aged ≥6 years due to reliability of testing) according to Global Lung Function Initiative standards; (iv) presence of clinically important bacterial pathogens (e.g., *Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia cepacia* complex, and *Aspergillus* spp.); and (v) body mass index (BMI) as reported by providers. CF complications and comorbidities, including prevalence of sinus disease, prevalence of CF-related diabetes, incidence of gallstones/cholecystectomy, prevalence of depression, prevalence of anxiety, and prevalence of hypertension, and liver function test (LFT) abnormalities were assessed as safety outcomes. Death and lung transplantation were also evaluated.

2.3. Statistical analyses

2.3.1. Analyses of CF disease progression and safety outcomes

Outcome measures were summarized descriptively for each of the 5 years before the index date and each of the 2 years after the index date; the results were plotted by year to visually illustrate the trends in outcomes over time. For continuous outcomes (e.g., $ppFEV_1$) for each analysis year – if more than one measure was available during the year for a person – all available measurements were averaged within person, then across people in the cohort to produce an overall mean for the study cohort for that year. For dichotomous outcomes (yes/no) for each analysis year, the proportions of people with that outcome recorded as present in the registry in that analysis year were quantified. For the laboratory measurements (LFTs and bacterial pathogens), patients with ≥1 LFT elevation during each 1-year time period and any positive bacterial culture results were included in the numerator for prevalence calculations.

The year (365 days) immediately preceding treatment initiation was considered the baseline year for calculation of change from baseline for continuous outcomes ($ppFEV_1$, BMI) as well as change from baseline in the mean number of PEx and hospitalizations per patient per year.

Proportions of people with CF with ≥1 PEx and ≥1 hospitalization (and corresponding 95% confidence intervals [CIs]), as well as annualized mean number of PEx and hospitalization events (and corresponding 95% CIs), were calculated for each of the 5 years before treatment and for each year after ELX/TEZ/IVA initiation, taking exposure duration into account. Percent reduction in PEx and hospitalization frequency from baseline year were calculated using the following formula:

$$\%\ \text{reduction in mean number of events per person per year} = [(\text{mean per patient per year in baseline year}) - (\text{annualized mean per patient per year post-treatment})]/(\text{mean per patient per year in baseline year}) * 100$$

Analyses of lung function included calculating summary statistics (mean and 95% CIs) for $ppFEV_1$ for each year of the 5-year pre-treatment period and for each year following ELX/TEZ/IVA initiation. The $ppFEV_1$ value for each year for each person was calculated as the average of all available values for that year measured in the clinic setting, then averaged across people in the cohort to produce an overall mean for the study cohort for that year. Mean change in $ppFEV_1$ from the baseline year and corresponding 95% CIs were also calculated. BMI analyses were performed in a similar manner to the lung function analyses.

Percentages of people with CF with evaluated bacterial pathogens, CF complications and comorbidities, and LFT abnormalities were calculated for each year of the 5-year pre-treatment period and each year after ELX/TEZ/IVA initiation.

For $ppFEV_1$, PEx, and all-cause hospitalization, analyses were also conducted by genotype subgroups (homozygous for *F508del-CFTR* [*F*/*F*], heterozygous for *F508del-CFTR* and a minimal function mutation [*F*/MF], heterozygous for *F508del-CFTR* and a residual function mutation [*F*/RF], and heterozygous for *F508del-CFTR* and a gating mutation [*F*/G]), baseline lung function subgroups (<40, ≥40 to 70, and ≥70), and prior CFTR modulator exposure history subgroups (CFTR-modulator-naïve vs. previously treated). A sensitivity analysis was conducted for the outcome of BMI in the subgroup of patients who were aged ≥18 years at ELX/TEZ/IVA initiation.

2.3.2. Death and lung transplantation analyses

The outcomes of death and lung transplantation were evaluated in the entire study population of all people with CF, regardless of age or genotype, with a record of ELX/TEZ/IVA initiation in the US CFFPR between October 21, 2019 and December 31, 2020, who were followed through December 31, 2021, loss of follow-up, or treatment discontinuation. The percentages of people with CF who died or had lung transplantation following the index date were quantified and person-time of follow-up for each patient was considered to estimate the annualized rate, which was then compared with the period before ELX/TEZ/IVA availability (2019 CFFPR data for all people with CF aged ≥12 years with ≥1 *F508del* allele, representing the population who would initially become eligible for ELX/TEZ/IVA treatment). Person-time was calculated as the time from the index date until the time of death, lung transplantation (for lung transplantation outcome only), treatment discontinuation, or loss to follow-up, whichever occurred first.

All analyses were descriptive and no statistical hypothesis testing was performed. No imputation of missing data was conducted.

3. Results

3.1. Cohort characteristics

Overall, 16,116 people with CF who initiated ELX/TEZ/IVA treatment between October 21, 2019 and December 31, 2020 in the United States were included in the initial study cohort. Mean age at ELX/TEZ/IVA initiation was 27.4 years (standard deviation, 12.7; median [interquartile range (IQR)], 24.8 [17.7, 34.2]); 52.1% were male and 98.9% had ≥1 *F508del-CFTR* allele (*F*/*F* genotype 54.7%, *F*/MF genotypes 25.0%, *F*/RF genotypes 8.3%, *F*/G genotypes 3.9%) (Table 1). There were 5.5% of people in the cohort who had an *F508del* allele with another known mutation, 1.6% who had an *F508del* allele with an unknown mutation, and 1.1% who had no recorded *F508del* allele or were missing genotype information in the registry. Mean treatment duration was 20.4 months (median [IQR] 23.0 [19.0, 24.0]) at the time of this interim analysis and 60.9% of the cohort had a prior history of CFTR modulator use. There were 1035 patients (6.4%) who met the study definition for treatment discontinuation during the post-treatment period.

Table 1
Baseline characteristics for the US ELX/TEZ/IVA cohort.

Characteristic	US ELX/TEZ/IVA cohort (n = 16,116)
Age at ELX/TEZ/IVA initiation, mean (SD), years	27.4 (12.7)
Age at ELX/TEZ/IVA initiation, median (IQR), years	24.8 (17.7, 34.2)
Age categories, %	
<12 years	1.4
≥12 to <18 years	24.6
≥18 years	73.9
Sex, %	
Male	52.1
Female	47.9
Race, %	
White	96.0
Other (non-missing)	4.0
Ethnicity, %	
Hispanic	6.2
Non-Hispanic	90.4
Unknown/missing	3.4
Genotype, %	
F/*F*	54.7
F/MF	25.0
F/RF	8.3
F/G	3.9
F/other known	5.5
F/unknown or missing	1.6
Other/unknown or missing	1.1
$ppFEV_1$, mean (SD), percentage points	72.1 (24.2)
$ppFEV_1$ categories, %	
<40	11.6
≥40 to <70	29.5
≥70 to <90	28.0
≥90	25.0
Unknown/missing	5.9
Prior history of CFTR modulator use, %	60.9

CFTR: cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; *F*/*F*: homozygous for *F508del-CFTR;* *F*/G: heterozygous for *F508del-CFTR* and a gating mutation; *F*/MF: heterozygous for *F508del-CFTR* and a minimal function mutation; *F*/RF: heterozygous for *F508del-CFTR* and a residual function mutation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SD: standard deviation; IQR: interquartile range.

A total of 11,951 of the 16,116 patients in the cohort (74.2%) had ≥1 clinical encounter in each of the 5 pre-treatment baseline years as well as in the post-treatment Years 1 and 2; this subgroup was the focus of analyses comparing post-treatment outcomes (PEx, hospitalizations, $ppFEV_1$, prevalence of bacterial pathogens, BMI, CF complications and comorbidities, and LFTs) to within-cohort patterns observed in the 5 years before treatment initiation. This subgroup was comparable to the overall cohort with regards to demographics and clinical characteristics (Supplementary Table S1); mean treatment duration was 22.7 months (median [IQR] 24.0 [22.0, 24.0]).

3.2. PEx and hospitalizations

In the subset of 11,951 people who had ≥1 clinical encounter in each of the 5 pre-treatment years as well as post-treatment, the percentage (95% CI) of patients with ≥1 PEx declined in Years 1 and 2 post-treatment (11.6% [11.1, 12.2] and 10.9% [10.3, 11.4], respectively) as compared to each of the years during the 5-year pre-treatment period (40.2% [39.4, 41.1] in Year −5, 40.5% [39.6, 41.4] in Year −4, 42.4% [41.5, 43.3] in Year −3, 43.3% [42.5, 44.2] in Year −2, and 42.7% [41.8, 43.6] in baseline Year −1) (Fig. 1A). Similarly, the mean number of PEx per patient per year (95% CI) declined following treatment initiation and was 0.18 (0.17, 0.19) in post-treatment Year 1 and 0.18 (0.17, 0.19) in Year 2, as compared to 0.72 (0.70, 0.74) in Year −5, 0.76 (0.74, 0.78) in Year −4, 0.81 (0.79, 0.83) in Year −3, 0.83 (0.81, 0.85) in Year −2, and 0.86

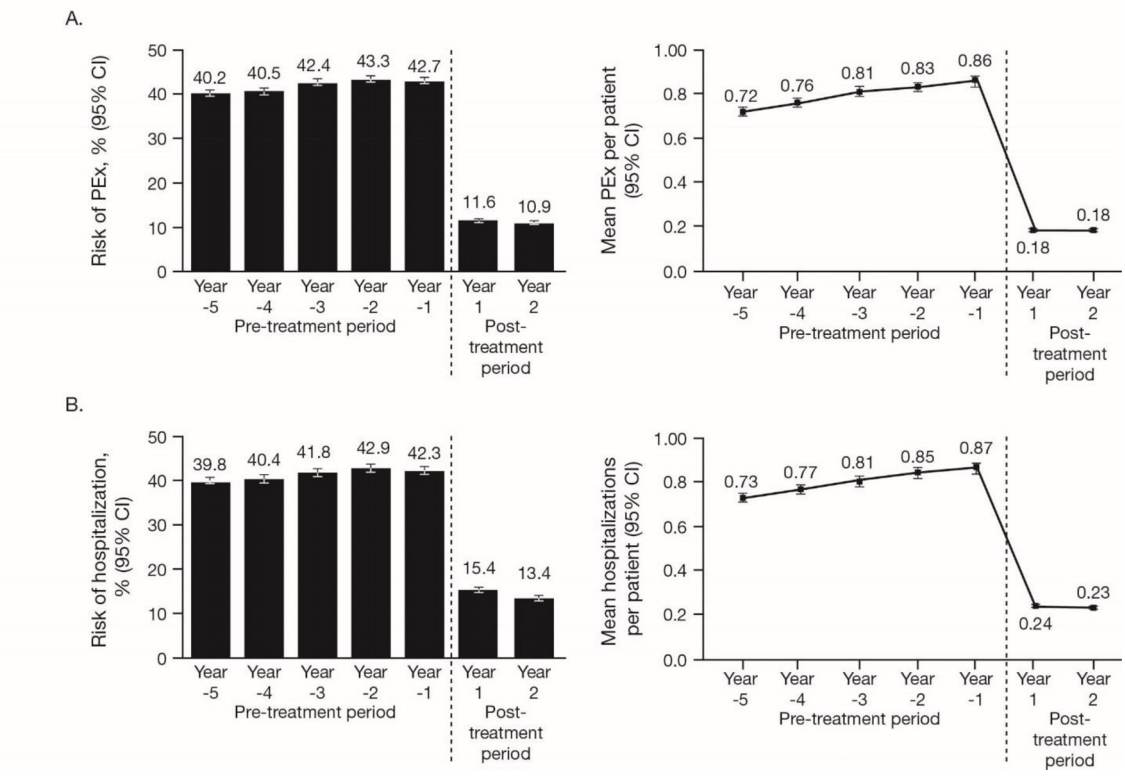

Fig. 1. PEx and hospitalization by year in people with CF treated with ELX/TEZ/IVA (n = 11,951). (A) Risk of PEx in subgroup with 5 years of non-missing pre-treatment data; (B) risk of hospitalization for any reason in subgroup with 5 years of non-missing pre-treatment data.
For both outcomes, annualized mean is presented to account for variable exposure duration during the post-treatment period.
CF: cystic fibrosis; CI: confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; PEx: pulmonary exacerbations.

(0.83, 0.88) in baseline Year −1 (Fig. 1A). The percent reduction in the mean number of PEx was estimated at 79% in Year 2 compared to the baseline year. Similar declines in PEx were observed across genotype subgroups, subgroups of people with CF with mild to moderate and severe lung function impairment at baseline, and subgroups of people with CF with and without prior CFTR modulator use (Supplementary Fig. S1, S2, and S3).

In the same subset, the percentage (95% CI) of patients with ≥1 hospitalization declined to 15.4% (14.8, 16.1) in Year 1 and 13.4% (12.8, 14.0) in Year 2 post-treatment, as compared to 39.8% (38.9, 40.7) in Year −5, 40.4% (39.6, 41.3) in Year −4, 41.8% (40.9, 42.7) in Year −3, 42.9% (42.0, 43.8) in Year −2, and 42.3% (41.4, 43.2) in baseline Year −1 (Fig. 1B). The mean number of hospitalizations per patient per year (95% CI) declined following treatment initiation to 0.24 (0.23, 0.25) in Year 1 and 0.23 (0.22, 0.24) in Year 2, as compared to 0.73 (0.71, 0.75) in Year −5, 0.77 (0.75, 0.79) in Year −4, 0.81 (0.78, 0.83) in Year −3, 0.85 (0.82, 0.87) in Year −2, and 0.87 (0.84, 0.89) in baseline Year −1 (Fig. 1B). The percent reduction in the mean number of hospitalizations was estimated at 74% in Year 2 compared to the baseline year. Declines in hospitalization were also observed in genotype subgroups, subgroups of people with CF with mild to moderate and severe lung function impairment at baseline, and subgroups of people with CF with and without prior CFTR modulator use (Supplementary Fig. S4, S5, and S6).

3.3. Lung function

Overall, 9381 people with CF had ≥1 evaluable lung function measurement available in each of the 5 years before ELX/TEZ/IVA initiation and in Years 1 and 2 following treatment initiation.

In this subset, mean $ppFEV_1$ declined continuously in the 5-year pre-treatment period (77.1 in Year −5, 76.0 in Year −4, 74.6 in Year −3, 73.7 in Year −2, and 72.7 in baseline Year −1), but then increased significantly after treatment initiation to 80.9 in Year 1 (8.2 percentage points [95% CI: 8.0, 8.4] increase compared to baseline Year −1) and 81.6 in Year 2 (8.9 percentage points [95% CI: 8.7, 9.1] increase compared to baseline Year −1 (Fig. 2). In an analysis of a larger subset of 11,632 people only requiring availability of evaluable $ppFEV_1$ data in baseline Year −1 (rather than each of 5 years pre-treatment), the results were consistent ($ppFEV_1$ increased by 8.7 percentage points [95% CI: 8.5, 8.9] from baseline to Year 2).

Improvements in lung function were observed in all evaluated genotype subgroups (Supplementary Fig. S7). Mean change from baseline (Year −1) to Year 2 in $ppFEV_1$ was 10.1 percentage points (95% CI: 9.7, 10.5) for people with an *F*/MF genotype, 9.4 percentage points (95% CI: 9.1, 9.6) for people with the *F*/*F* genotype, 4.9 percentage points (95% CI: 4.1, 5.8) for people with an *F*/G genotype, and 2.2 percentage points (95% CI: 1.6, 2.8) for people with an *F*/RF genotype. Results were also consistent with the overall cohort in subgroups of people with CF with mild to moderate and severe lung function impairment at baseline, and subgroups of people with CF with and without prior CFTR modulator use (Supplementary Fig. S8 and S9).

3.4. Bacterial pathogens

Among people with ≥1 encounter in each of the 5 years before treatment initiation and in the post-treatment period, 98.4% had available bacterial cultures during the year before treatment initiation. In the post-treatment period, which coincided with the SARS-CoV-2 pandemic, the availability of bacterial culture was 87.8% in

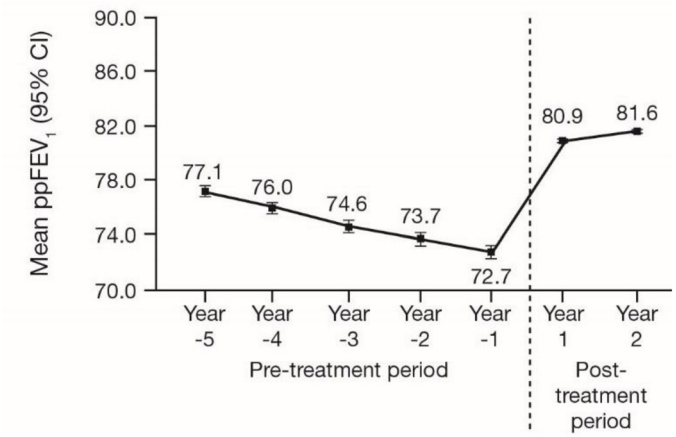

Fig. 2. Mean ppFEV$_1$ by year in people with CF treated with ELX/TEZ/IVA (n = 9381).
CF: cystic fibrosis; CI: confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; ppFEV$_1$: percent predicted forced expiratory volume in 1 second.

Year 1 and 89.0% in Year 2. Analyses of bacterial pathogens focused on the 9311 people with CF for whom bacterial cultures were available in each of the 5 years before ELX/TEZ/IVA initiation and following treatment initiation. Reductions in the prevalence of all evaluated pathogens, including *P. aeruginosa, S. aureus, B. cepacia* complex, and *Aspergillus,* were observed following ELX/TEZ/IVA initiation (Fig. 3).

3.5. BMI

A total of 11,081 people in the study cohort had ≥1 BMI measurement in each of the 5 years before treatment initiation and in the post-treatment Years 1 and 2. Mean BMI increased from 22.1 kg/m^2 (95% CI: 22.0, 22.2) in the baseline year to 23.6 kg/m^2 (95% CI: 23.6, 23.7) in Year 2 following ELX/TEX/IVA treatment (mean increase 1.6 kg/m^2 [95% CI: 1.5, 1.6]) (Supplementary Fig. S10A). Results were consistent with sensitivity analyses in the subgroup of people who were aged ≥18 years at ELX/TEZ/IVA treatment initiation date (Supplementary Fig. S10B).

3.6. CF complications and comorbidities, and LFTs

No new safety concerns were identified during the interim analysis period. CF complications and comorbidities (including si-

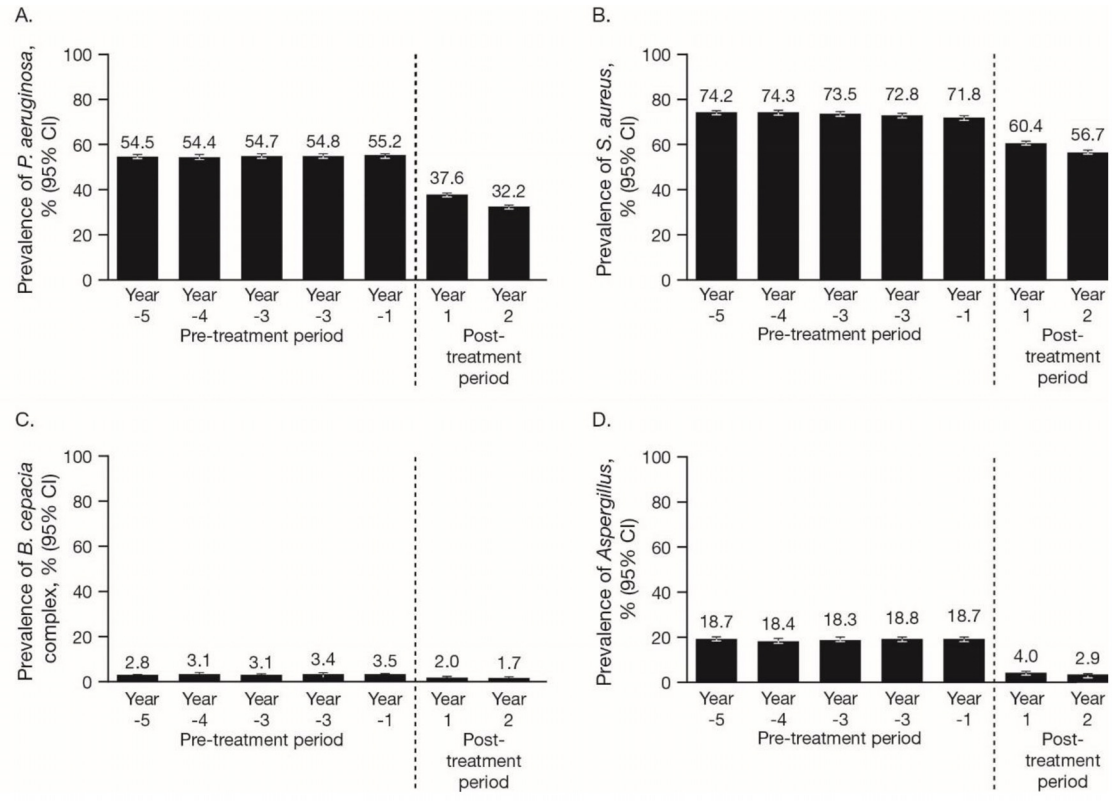

Fig. 3. Prevalence of selected pulmonary pathogens of (A) *Pseudomonas aeruginosa*, (B) *Staphylococcus aureus*, (C) *Burkholderia cepacia* complex, and (D) *Aspergillus* by year in people with CF treated with ELX/TEZ/IVA (n = 9311).
CF: cystic fibrosis; CI: confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor.

Table 2
Annual rate of death and lung transplantation following ELX/TEZ/IVA initiation relative to historical data (2019) from the US CFFPR.

Outcome	ELX/TEZ/IVA cohort			2019 historical cohort[a]			Estimated reduction relative to historical data, %
	Events, n	Person-time, years	Annualized rate, % (95% CI)	Events, n	Patients, n	2019 rate, %	
Death	130	27,890.87	0.47 (0.39, 0.55)	314	19,013	1.65	**72**
Lung transplantation	45	27,889.21	0.16 (0.12, 0.22)	205	19,013	1.08	**85**

[a] Patients with ≥1 *F508del-CFTR* allele who were aged ≥12 years.
CFFPR: Cystic Fibrosis Foundation Patient Registry; CI: confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor.

nus disease, CF-related diabetes, gallstones/cholecystectomy, depression, anxiety, and hypertension) were generally comparable between the pre-treatment period and following ELX/TEZ/IVA initiation or increased consistent with age-related CF disease progression (Supplementary Fig. S11). For instance, while there was a small numerical increase in the prevalence of depression (24.3% during the pre-treatment baseline year, 25.6% in Year 1, and 27.8% in Year 2), increases of similar or greater magnitude were observed in each of the pre-treatment years (Supplementary Fig. S11C). A similar pattern was observed for CF-related diabetes, anxiety disorders, and hypertension, where prevalence increased numerically in each of the 5 years prior to ELX/TEZ/IVA initiation and in the post-treatment period consistent with aging and CF disease progression (Supplementary Fig. S11B, D, and F).

Among people in the study cohort with available LFT results ($n = 7506$), the proportion who had alanine transaminase and aspartate transaminase elevations >3 ×, >5 ×, or >8 × the upper limit of normal was generally comparable between the pre-treatment and post-treatment periods; the frequency of bilirubin elevations >2 × the upper limit of normal was higher in the post-treatment period, consistent with clinical study results and the product label (Supplementary Fig. S12).

3.7. Death and lung transplantation

Of the 16,116 people with CF who initiated ELX/TEZ/IVA, 0.52% ($n = 83$) died in Year 1 and 0.33% ($n = 47$) of the remaining cohort died in Year 2. Additionally, 0.19% ($n = 31$) had lung transplantation in Year 1 and 0.10% ($n = 14$) of the remaining cohort had lung transplantation in Year 2. The annualized rate of death for the full post-treatment period was 0.47% (95% CI: 0.39, 0.55) and the annualized rate of lung transplantation for the full post-treatment period was 0.16% (95% CI: 0.12, 0.22). Compared to 2019 US CFFPR data for people with CF aged ≥12 years who had ≥1 *F508del* allele, these estimates were 72% lower for death (1.65% died in 2019) and 85% lower for lung transplantation (1.08% had a lung transplant in 2019) (Table 2).

4. Discussion

This is the largest real-world study of outcomes among people with CF treated with ELX/TEX/IVA. In this interim analysis, people with CF taking ELX/TEZ/IVA had a reduced frequency of PEx and improved lung function, with a lower frequency of all-cause hospitalizations, lower prevalence of positive bacterial cultures, and increased BMI. Most notably, the post-treatment annualized rate of death and lung transplantation was 72% and 85% lower, respectively, compared to what was observed in the historical population.

As PEx are associated with declining lung function, reduced quality of life, and increased mortality [16], decreasing the frequency of PEx episodes is a key goal in treatment for people with CF. Following ELX/TEZ/IVA treatment initiation, the annualized mean number of PEx events declined by 79% in the first post-treatment year compared to the year before and this decline was sustained in post-treatment Year 2, with similar trends observed across genotype subgroups. This decline in the frequency of PEx is particularly noteworthy since, in the 5-year period before ELX/TEZ/IVA treatment, the mean number of events per patient per year increased numerically each year.

ELX/TEZ/IVA treatment also led to sustained and clinically meaningful increases in $ppFEV_1$ in the real-world setting. The fact that the mean change in $ppFEV_1$ from baseline observed in Year 1 was similar to that in Year 2 (8.2 and 8.9 percentage points, respectively) demonstrates that the improvements in lung function with ELX/TEZ/IVA treatment are durable over time, consistent with results that are emerging from long-term clinical extension studies [12,13]. While the magnitude of change in $ppFEV_1$ is not directly comparable between real-world and clinical studies due to differences in study populations and assessments, frequency of visits, and other factors, the improvements in $ppFEV_1$ by genotype observed in this study were broadly consistent with what has been reported in ELX/TEZ/IVA Phase 3 clinical trials (14.3, 10.0, and 3.7 percentage points in people with an *F*/MF genotype, *F/F* genotype, and *F*/G and *F*/RF genotypes, respectively) [8,9,17].

Improvements in outcomes beyond those evaluated in the Phase 3 studies were also observed following ELX/TEZ/IVA initiation. The frequency of all-cause hospitalizations declined after treatment initiation by 74% and the prevalence of all evaluated bacterial pathogens was lower. Although decreases in some pulmonary pathogens (e.g., *P. aeruginosa*) have previously been reported in the long-term registry-based studies of other CFTR modulators [18], this is the first study to show declines across all evaluated pulmonary pathogens after initiating therapy. This result suggests that highly effective modulator therapies, such as ELX/TEZ/IVA, may reduce susceptibility to chronic lung infections by altering lower airway microbiology [19]. ELX/TEZ/IVA treatment also led to a small increase in BMI during the first year of this study, consistent with Phase 3 clinical studies in children, adolescents, and adults with CF; results were consistent in the overall population and in sensitivity analyses in the subgroup of people who were aged ≥18 years at the time of ELX/TEZ/IVA initiation.

Given the improved lung function, reductions in bacterial pathogens, and increased BMI seen in people with CF taking ELX/TEZ/IVA in this study and in previous clinical trials [8–10], we sought to understand potential impacts on survival and lung transplantation. Although survival and lung transplantation reductions have been reported for other CFTR modulators [18], this is the first study to systematically evaluate the incidence of death and lung transplantation among people with CF treated with ELX/TEZ/IVA and to demonstrate dramatic declines in both outcomes following start of therapy. These results suggest ELX/TEZ/IVA treatment can modify the course of CF disease progression, with future analyses from this study with longer follow-up expected to offer further insights.

There were no new safety concerns identified during this interim analysis. LFTs and CF complications and comorbidities were generally consistent between the 5-year pre-treatment period and

the first year following ELX/TEZ/IVA initiation. While people with CF experience depression and anxiety at a rate 2–3 × greater than the general population [20], the prevalence of depression and anxiety disorders after ELX/TEZ/IVA initiation was consistent with patterns observed during pre-treatment years.

Some limitations of the current study should be considered. We analyzed data collected during routine clinical practice, where there are no standardized assessments as is common in clinical studies with primary data collection. Imputation was not conducted for missing data in this study and, although we attempted to compare risk of death and transplantation to a historical population that represented the population who first became eligible for ELX/TEZ/IVA, we acknowledge that there could be residual confounding due to differences in the historical (comparison) population compared to our study population. However, the baseline demographics of the patients in this study are similar to those of the historical (comparison) population, suggesting that confounding may be limited. Our analyses of disease progression outcomes required the availability of 5 years of pre-treatment outcome data for each participant and not all people with CF had retrospective data available. However, we also conducted analyses that required availability of only 1 year of pre-treatment outcome data for each participant and the findings were consistent with the results presented here. Additionally, for patients who met the definition of treatment discontinuation during the study, the reason for discontinuation was not available from the patient registry.

This interim analysis overlapped with the SARS-CoV-2 pandemic, in which social distancing, restrictions on social interactions, and mask use might have partially impacted on some of the observed clinical outcome patterns, including PEx [21]. However, clinical studies of ELX/TEZ/IVA completed before the start of the pandemic reported similar robust decreases in the frequency of PEx [8–10,12]. In addition to clinical studies, Dwight and Marshall previously reported a 61% reduction in PEx in the CFFPR among people with CF aged ≥12 years following ELX/TEZ/IVA approval, but before the onset of the pandemic [22], and a smaller study performed during the pandemic period observed reductions in PEx rates that were significantly more pronounced in the population treated with ELX/TEZ/IVA compared to those who were not (80.2% reduction vs. 29.5% reduction, respectively) [23]. While the SARS-CoV-2 pandemic could have partially impacted on PEx frequency, other outcomes should not be similarly affected (e.g., change in ppFEV$_1$, death, or organ transplantation) and these outcomes also showed clear clinical benefits consistent with ELX/TEZ/IVA Phase 3 clinical trials.

5. Conclusions

Results from this interim analysis of an ongoing 5-year observational registry-based study support the positive benefit-risk profile of ELX/TEZ/IVA established in the Phase 3 clinical trials, with no new safety concerns identified. Improvements were seen in a broad range of clinically important outcomes in the first post-treatment year that were maintained into the second post-treatment year, suggestive of CF disease modification with ELX/TEZ/IVA treatment. Furthermore, this is the largest study to report an association between ELX/TEZ/IVA use and decreases in the incidence of death and lung transplantation. Future analyses from this study will provide additional insight into the long-term effects of ELX/TEZ/IVA treatment in the real-world setting.

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Credit authorship contribution statement

All authors were involved in the design of the study and data were collected by the US CFFPR. All authors participated in the analysis and interpretation of study data. The manuscript was drafted by Julie K. Bower and Nataliya Volkova, and all authors contributed to critical revision of the manuscript for important intellectual content and gave final approval of the manuscript for publication.

Declaration of Competing Interest

Julie K. Bower, Nataliya Volkova, Neil Ahluwalia, Gurvaneet Sahota, Fengjuan Xuan, Anna Chin, and Tanya G. Weinstock are employees of Vertex Pharmaceuticals and may own stock or stock options in that company. Josh Ostrenga and Alexander Elbert are employees of the Cystic Fibrosis Foundation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.03.002.

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