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Research article

Real-world effectiveness of elexacaftor/tezacaftor/ivacaftor on the burden of illness in adolescents and adults with cystic fibrosis

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A R T I C L E I N F O

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A B S T R A C T

Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been shown to be safe and efficacious in people with cystic fibrosis (CF) aged ≥2 years. Here, we describe results from an observational study assessing change in burden of illness following initiating ELX/TEZ/IVA in real-world settings.

Methods: This US-based, multicenter, observational study used data from electronic medical records to evaluate real-world burden of illness before and after ELX/TEZ/IVA initiation in people with CF aged ≥12 years heterozygous for *F508del* and a minimal function mutation (*F*/MF) or an uncharacterized *CFTR* mutation. Endpoints included absolute change from baseline in percent predicted forced expiratory volume in 1 s ($ppFEV_1$), body mass index (BMI) and BMI-for-age z-score, glycated hemoglobin (HbA1c), and numbers of pulmonary exacerbations (PEx).

Results: Overall, 206 people with CF were enrolled (mean [SD] age 22.5 [11.1] years; 192 [93.2%] with *F*/MF genotype). Mean follow-up was 15.6 (SD, 1.6) months. Improvements in $ppFEV_1$ (7.3 [95% CI: 5.7, 8.8] percentage points) were observed from baseline through follow-up. Increases in BMI (1.40 [95% CI: 1.07, 1.77] kg/m^2) and BMI-for-age z-score (0.14 [95% CI: 0.00, 0.28]) were also observed from baseline at 12 months. The estimated annualized rate of any PEx was 1.31 at baseline and 0.61 over follow-up (rate ratio 0.47 [95% CI: 0.39, 0.55]), with annualized rates of PEx requiring antibiotics and hospitalizations of 0.55 and 0.88 in the baseline period and 0.12 and 0.36 over follow-up (rate ratios 0.22 [95% CI: 0.15, 0.31] and 0.41 [95% CI: 0.32, 0.51]), respectively. Absolute change in HbA1c was −0.22 (95% CI: -0.38, −0.06) from baseline through follow-up.

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Conclusions: ELX/TEZ/IVA treatment was associated with improved lung function, increased BMI, reduced frequency of PEx, and improved (i.e., reduced) HbA1c. These results confirm the broad clinical benefits of ELX/TEZ/IVA seen in clinical trials and show the potential for ELX/TEZ/IVA to improve markers of glucose metabolism.

Abbreviations

BMI	body mass index
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
ELX	elexacaftor
EMR	electronic medical record
F/MF	heterozygous for F508del-CFTR and a minimal function mutation
HbA1c	glycated hemoglobin
IVA	ivacaftor
PEx	pulmonary exacerbations
ppFEV1	percent predicted forced expiratory volume in 1 s
SD	standard deviation
TEZ	tezacaftor

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease that is 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 [1,2]. Clinically, CF manifests as a multisystemic disease with respiratory, pancreatic, hepatic, and gastrointestinal dysfunctions appearing early in life [3–5]. Progressive loss of lung function is the leading cause of mortality in people with CF, with obstruction of airways with thick mucus, chronic bacterial infection of airways, and damaging lung inflammatory responses leading to irreversible structural lung changes [6].

While there is no cure for CF and patients experience substantial disease burden, the treatment landscape has significantly changed in the past decade with the emergence of CFTR modulator therapies. 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 [7,8]. A 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 at least one *F508del-CFTR* allele [9–11]. The *F508del-CFTR* mutation is the most common *CFTR* mutation, with nearly 90% of people with CF in some regions of the world having at least one *F508del-CFTR* allele [12]. 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 s [$ppFEV_1$]), 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* [13]. These results demonstrated that ELX/TEZ/IVA is a superior treatment option for people with CF with at least one *F508del-CFTR* allele.

While the results from clinical trials and open-label extension studies [14,15] have established the efficacy and safety of ELX/TEZ/IVA, it is also important to understand the impact of ELX/TEZ/IVA under real-world conditions of use. Here, we report results from an observational study that assessed changes in real-world burden of illness in adolescents and adults with CF before and after starting treatment with ELX/TEZ/IVA.

2. Methods

2.1. Study objective, design, and population

HELIO (VX19-CFD-003) was a US-based, multicenter, longitudinal observational study designed to evaluate real-world burden of illness in people with CF aged ≥6 years before and after treatment with ELX/TEZ/IVA in real-world clinical settings. The study included two cohorts: (i) people with CF aged ≥12 years either heterozygous for *F508del* and a minimal function mutation (*F*/MF genotypes) or heterozygous for *F508del* and an uncharacterized *CFTR* mutation (*F*/uncharacterized genotypes) and (ii) children with CF aged 6 through 11 years who were homozygous for *F508del* or who had an *F*/MF or *F*/uncharacterized genotype. For this study, the

F/uncharacterized genotype was defined as participants with an *F508del* mutation with a second *CFTR* allele carrying a mutation not characterized as *F508del*, minimal function, gating, or residual function. Results from the first cohort (people with CF aged ≥12 years) are reported here; data collection and analysis were still ongoing for the second cohort (children with CF aged 6 through 11 years). Participants had ≥12 months of medical history available in the electronic medical record (EMR) and were excluded if they were enrolled in any interventional studies or had been enrolled in one within the past 28 days and their last exposure to investigational VX-445 (ELX) or VX-659 was <12 months prior to initial prescription of ELX/TEZ/IVA.

Data from the participants' EMRs were collected based on predefined windows relative to participants' treatment initiation dates (Fig. 1). Retrospective data were collected during the 12 months before ELX/TEZ/IVA treatment and prospective data were collected up to 16 months after initiation of ELX/TEZ/IVA. The baseline period was defined as the 12 months before ELX/TEZ/IVA initiation to the day of ELX/TEZ/IVA initiation. The post-ELX/TEZ/IVA follow-up period was defined as the time from the day after ELX/TEZ/IVA initiation to the completion of study participation or ELX/TEZ/IVA discontinuation, whichever occurred first.

2.2. Study outcomes

Endpoints were assessed through the pre- and post-ELX/TEZ/IVA treatment periods using data collected from the participants' EMRs. Endpoints included absolute change from baseline in ppFEV$_1$, number of any pulmonary exacerbations (PEx) compared to baseline (annualized event rate), number of PEx requiring either intravenous antibiotics or hospitalization compared to baseline (annualized event rates), absolute change in body mass index (BMI) and BMI-for-age z-score (BMI z-score) from baseline, and absolute change from baseline in glycated hemoglobin (HbA1c). Any PEx was defined as a visit with diagnosis codes for CF with pulmonary manifestations or respiratory infection and diagnosis codes for other gastrointestinal manifestations of CF or CF with other manifestations and at least one of the following: hospitalization, intravenous antibiotic within 24 h of admission or visit, or oral antibiotic (prescription given within 7 days of an outpatient visit with a diagnosis code of CF). Prescription orders were reviewed if they were prescribed for chronic or acute use. Those prescribed for chronic use were not considered per the operational definition of PEx. PEx requiring hospitalization was defined as PEx with an inpatient stay. PEx with intravenous antibiotics was defined as a PEx with an EMR identifying intravenous antibiotics within 24 h of admission or visit.

2.3. Statistical analyses

Baseline measurements were summarized descriptively with mean, standard deviation (SD), median, and interquartile range for continuous variables, and frequency and percentage for categorical variables. Summary statistics and two-sided 95% confidence intervals (CIs) were calculated for absolute changes from baseline at 6 months and 12 months and average change from baseline through the post-ELX/TEZ/IVA treatment period (up to 16 months). For each endpoint, the baseline was defined as the most recent non-missing measurement collected on or before initiation of ELX/TEZ/IVA. The values at 6 months and 12 months were defined as the most recent non-missing measurement closest to the 6-month study day and 12-month study day within the 6 (±3) and 12 (±3) month intervals after initiating ELX/TEZ/IVA. The absolute changes from baseline through the post-ELX/TEZ/IVA treatment period were calculated for ppFEV$_1$, BMI, BMI z-score (for patients aged ≤20 years at baseline), and HbA1c, and were defined as change from baseline to the average of all data points in the post-ELX/TEZ/IVA treatment period.

PEx endpoints were calculated as annualized event rates based on all available data and analyzed as the ratio of the annualized event rate during the post-ELX/TEZ/IVA period over the baseline rate during the pre-ELX/TEZ/IVA period. The rate ratios for any PEx, PEx requiring intravenous antibiotics, and PEx requiring hospitalization were calculated as the annualized event rate during the post-ELX/TEZ/IVA period over the annualized event rate during the baseline period (i.e., during the pre-ELX/TEZ/IVA period). A negative binomial model was used to estimate the annualized rate ratio during the pre- and post-ELX/TEZ/IVA periods. For the pre- and post-ELX/TEZ/IVA periods, the annualized rates per participant-year were determined; rates were calculated as the sum total across all participants of the number of PEx during each period divided by the sum total across all participants of the time in years. PEx events occurring within 30 days of a prior PEx were collapsed and considered as one PEx. All analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

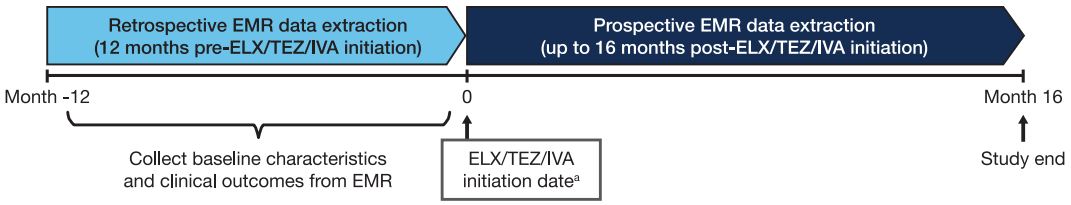

Fig. 1. Study design. Data on clinical characteristics and outcomes were extracted from the EMRs of each participant for the 12-month period prior to initiation of ELX/TEZ/IVA and for up to 16 months following initiation of ELX/TEZ/IVA. [a]ELX/TEZ/IVA prescription date. ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; EMR: electronic medical record.

Table 1
Baseline demographics and clinical characteristics of the HELIO aged ≥12 years cohort.

Characteristic[a]	ELX/TEZ/IVA (n = 206)
Age at index date, years, mean (SD)	22.5 (11.1)
Age categories, n (%)	
≥12 to <18 years	92 (44.7)
≥18 years	114 (55.3)
Sex, n (%)	
Male	107 (51.9)
Female	99 (48.1)
Genotype, n (%)	
F/MF	192 (93.2)
F/uncharacterized[b]	14 (6.8)
Baseline ppFEV$_1$, percentage points, mean (SD)	78.4 (24.3)
Baseline ppFEV$_1$ categories, n (%)[c]	
<40	16 (8.6)
≥40 to <70	47 (25.4)
≥70 to <90	62 (33.5)
≥90	60 (32.4)
Baseline weight, kg, mean (SD)	58.3 (15.1)
Baseline height, cm, mean (SD)	162.8 (11.1)
Baseline BMI, kg/m^2, mean (SD)[c]	21.7 (3.8)
Baseline BMI z-score, kg/m^2, mean (SD)[d]	0.1 (0.9)
Medical history, n (%)[e]	
Distal ileal obstruction syndrome	3 (1.5)
CF-related diabetes	56 (27.2)
CF liver disease	10 (4.9)
Pancreatic insufficiency	79 (38.3)
Chronic kidney disease	2 (1.0)
Prior medication use, n (%)[f]	199 (96.6)
Dornase alfa	153 (74.3)
Antibiotics	180 (87.4)
Bronchodilator	72 (35.0)
Hypertonic saline	132 (64.1)
Corticosteroids[g]	145 (70.4)
Insulin	42 (20.4)
Concomitant medication use, n (%)[h]	186 (90.3)
Dornase alfa	144 (69.9)
Antibiotics	138 (67.0)
Bronchodilator	59 (28.6)
Hypertonic saline	118 (57.3)
Corticosteroids[g]	113 (54.9)
Insulin	40 (19.4)
Follow-up time post-ELX/TEZ/IVA index date, months, mean (SD)[i]	15.6 (1.6)

BMI: body mass index; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; ELX: elexacaftor; *F*/MF: heterozygous for *F508del-CFTR* and a minimal function mutation; IVA: ivacaftor; LUM: lumacaftor; ppFEV$_1$: percent predicted forced expiratory volume in 1 s; SD: standard deviation; TEZ: tezacaftor.

[a] Baseline was defined as the most recent non-missing measurement on or before the ELX/TEZ/IVA index date.

[b] "*F*/uncharacterized" was defined as participants with an *F508del* mutation and a second *CFTR* allele carrying a mutation not characterized as *F508del*, minimal function, gating, or residual function and who were not eligible for treatment with IVA, LUM/IVA, or TEZ/IVA until the approval of additional mutations in December 2020.

[c] Percentages were calculated based on the total number of participants with non-missing baseline data for the given variable.

[d] BMI z-score was restricted for patients aged 12–20 years and is based on the Centers for Disease Control and Prevention BMI-for-age charts, selected BMI (kg/m^2) z-scores, by sex and age (https://www.cdc.gov/growthcharts/zscore.htm).

[e] Medical history was collected during the baseline period, which was from 12 months before the ELX/TEZ/IVA index date to the day of ELX/TEZ/IVA index date.

[f] Prior medications include any medication that started before the ELX/TEZ/IVA index date, regardless of when it ended. Route of administration was collected for corticosteroids, antibiotics, and hypertonic saline.

[g] Corticosteroids included any corticosteroid noted in the EMR and their route of administration, including oral, intravenous/injectable, inhaled, other, and missing.

[h] Concomitant medications include medication continued or newly prescribed/dispensed on or after the index date for ELX/TEZ/IVA treatment (i.e., medication is ongoing or the stop date is on or after the index date for ELX/TEZ/IVA). Route of administration was collected for corticosteroids, antibiotics, and hypertonic saline.

[i] Defined as time (months) from the day after the first prescription of ELX/TEZ/IVA to final data extraction date or 16 months post-index date for ELX/TEZ/IVA, whichever occurs first.

3. Results

3.1. Participant disposition, demographics, and baseline characteristics

This study collected data from 15 integrated health systems in the US between December 16, 2019 and February 13, 2022. A total of 206 participants were enrolled in this observational study, of whom 192 (93.2%) had *F*/MF genotypes (Table 1; Table S1). Mean age at baseline was 22.5 years (SD, 11.1) and 48.1% of participants were female. The mean $ppFEV_1$ was 78.4 percentage points (SD, 24.3) and BMI was 21.7 kg/m^2 (SD, 3.8) at baseline. The mean length of follow-up was 15.6 months (SD, 1.6).

3.2. Lung function and PEx

Following initiation of ELX/TEZ/IVA, participants had increases in $ppFEV_1$ at 6 months that were sustained through the follow-up period. The mean absolute change in $ppFEV_1$ from baseline at 6 months was 7.8 percentage points (95% CI: 5.9, 9.8) and was 7.3 percentage points (95% CI: 5.7, 8.8) through the follow-up period (Table 2).

Treatment with ELX/TEZ/IVA resulted in a 53% lower annualized rate of PEx (rate ratio, 0.47; 95% CI: 0.39, 0.55) (Table 3). At baseline, the annualized rate of PEx was 1.31, with an annualized rate of PEx requiring intravenous antibiotics of 0.55 and an annualized rate of PEx requiring hospitalizations of 0.88. Following initiation of ELX/TEZ/IVA, the annualized rate of PEx decreased to 0.61 for the post-treatment period (rate ratio, 0.47; 95% CI: 0.39. 0.55) with the annualized rate of PEx requiring intravenous antibiotics and the annualized rate of PEx requiring hospitalization similarly decreasing to 0.12 (rate ratio, 0.22; 95% CI: 0.15, 0.31) and 0.36 (rate ratio, 0.41; 95% CI: 0.32, 0.51), respectively (Table 3).

3.3. BMI, BMI z-score, and HbA1c

Mean BMI and BMI z-scores increased following initiation of ELX/TEZ/IVA. The mean absolute change in BMI from baseline was 1.08 kg/m^2 (95% CI: 0.79, 1.37) at 6 months and was 1.40 kg/m^2 (95% CI: 1.04, 1.77) at 12 months, and the mean absolute change in BMI z-score was 0.15 (95% CI: 0.03, 0.27) at 6 months and 0.14 (95% CI: 0.00, 0.28) at 12 months (Table 2). The mean absolute change in HbA1c was −0.30 (95% CI: -0.64, 0.04) at 6 months and −0.22 (95% CI: -0.38, −0.06) through the follow-up period (Table 2).

4. Discussion

HELIO was a real-world, observational study that assessed the clinical effectiveness of ELX/TEZ/IVA in people with CF aged ≥6 years with either *F*/MF or *F*/uncharacterized genotypes in the US. Here, we described the results for participants aged ≥12 years and their improvement in burden of illness after initiating ELX/TEZ/IVA treatment. Improvements in lung function (assessed by change in $ppFEV_1$) and nutritional parameters (BMI and BMI z-score), along with reductions in PEx and HbA1c levels, were seen following the initiation of ELX/TEZ/IVA and were maintained through the follow-up period (up to 16 months), regardless of varying CF lung disease.

Table 2
Changes in $ppFEV_1$, BMI, BMI z-score, and HbA1c from baseline to follow-up after ELX/TEZ/IVA initiation.

	$ppFEV_1$, percentage points		BMI, kg/m^2		BMI z-score for participants aged 12–20 years		HbA1c, %	
Baseline[a], mean (SD)	n = 185	78.4 (24.3)	n = 202	21.74 (3.82)	n = 114	0.10 (0.94)	n = 144	6.07 (1.65)
Post-treatment[b], mean (SD)	n = 163	84.9 (25.0)	n = 197	22.92 (4.57)	n = 110	0.21 (0.96)	n = 140	5.83 (1.39)
Absolute change at 6 months[c], mean (95% CI)	n = 116	7.8 (5.9, 9.8)	n = 155	1.08 (0.79, 1.37)	n = 94	0.15 (0.03, 0.27)	n = 58	−0.30 (-0.64, 0.04)
Absolute change at 12 months[d], mean (95% CI)	n = 116	7.5 (5.6, 9.3)	n = 156	1.40 (1.04, 1.77)	n = 96	0.14 (0.00, 0.28)	n = 63	−0.31 (-0.62, 0.00)
Absolute change from baseline through follow-up[e], mean (95% CI)	n = 161	7.3 (5.7, 8.8)	n = 194	1.03 (0.80, 1.26)	n = 110	0.13 (0.04, 0.22)	n = 109	−0.22 (-0.38, −0.06)

BMI: body mass index; CI: confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; HbA1c: glycated hemoglobin; $ppFEV_1$: percent predicted forced expiratory volume in 1 s; SD: standard deviation.

[a] At baseline, the most recent non-missing measurements ($ppFEV_1$, BMI, BMI-for-age z-score, and HbA1c) on or before the ELX/TEZ/IVA index date.

[b] Average through post-ELX/TEZ/IVA period is defined as average of all measurements available a day after the first prescription of ELX/TEZ/IVA and up to final data extraction date or 16 months post-index date for ELX/TEZ/IVA, whichever occurs first.

[c] At 6 months, the most recent non-missing measurements ($ppFEV_1$, BMI, BMI-for-age z-score, and HbA1c) closest to the 6-month date and within the 6 ± 3 months (182 ± 91 days) window post-index date for ELX/TEZ/IVA.

[d] At 12 months, the most recent non-missing measurements ($ppFEV_1$, BMI, BMI-for-age z-score, and HbA1c) closest to the 12-month date and within the 12 ± 3 months (365 ± 91 days) window post-index date for ELX/TEZ/IVA.

[e] The average follow-up was 15.6 months.

Table 3
Annualized rate of pulmonary exacerbations after ELX/TEZ/IVA initiation.

	Any PEx	PEx with intravenous antibiotics	PEx with hospitalizations
Baseline annualized rate (pre-ELX/TEZ/IVA)[a]	1.31	0.55	0.88
Post-ELX/TEZ/IVA annualized rate[b]	0.61	0.12	0.36
Rate ratio (95% CI)[c]	0.47 (0.39, 0.55)	0.22 (0.15, 0.31)	0.41 (0.32, 0.51)

CI: confidence interval; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; PEx: pulmonary exacerbations.

[a] Pre-ELX/TEZ/IVA period is 12 months before and including the ELX/TEZ/IVA index date.

[b] Post-ELX/TEZ/IVA period is a day after the ELX/TEZ/IVA index date and up to final data extraction date or 16 months post-index date for ELX/TEZ/IVA, whichever occurs first.

[c] Rate ratio is annualized event rate during the post-ELX/TEZ/IVA period over the annualized event rate during the pre-ELX/TEZ/IVA period; 1 year is defined as 365 days. Estimated rate ratio and 95% CI are based on the negative binomial model.

CF is associated with substantial disease burden, with patients suffering from declines in lung function, respiratory infections, hospitalizations, and PEx, and the need for supplementary nutrition to maintain weight [16]. While clinical trials have demonstrated that ELX/TEZ/IVA is efficacious and safe in people with CF with at least one *F508del* allele, the current study was designed to assess the impact of ELX/TEZ/IVA usage on burden of illness (i.e., lung function, PEx, and glucose control) in people with CF in real-world settings.

Participants taking ELX/TEZ/IVA had improvements in respiratory function, as seen by increases in $ppFEV_1$, along with decreases in annualized rates of PEx, over the course of the 16-month follow-up period. While the increases in $ppFEV_1$ seen in this patient population were somewhat lower than those previously reported in the pivotal clinical trials (+7.3 percentage points through the follow-up period compared with +14.3 percentage points at week 24 [*F*/MF genotypes] and +10.0 percentage points at week 4 [homozygous for *F508del-CFTR* genotypes] in pivotal trials [9,10]), it is important to note that participants in the current study had differing degrees of CF lung disease at baseline, with a mean $ppFEV_1$ of 78.4 percentage points and nearly 33% of participants having $ppFEV_1$ >90 percentage points suggesting fairly well-preserved lung function at baseline. In contrast, participants with *F*/MF genotypes who took part in the 24-week pivotal trial of ELX/TEZ/IVA that formed the basis of the safety profile had a mean $ppFEV_1$ of 61.6 percentage points at baseline with only 1.0% of participants having $ppFEV_1$ >90 percentage points [9]. This would suggest that there was a higher proportion of participants in the clinical trials with more severe CF lung disease at baseline than in the current study. Interestingly, the mean increase in $ppFEV_1$ reported here is consistent with increases recently reported in an analysis of >16,000 patients from the US Cystic Fibrosis Foundation Patient Registry (+7.8 percentage points) who had been taking ELX/TEZ/IVA for up to 2 years [17]. Taken together, these real-world results not only confirm findings from clinical trials showing ELX/TEZ/IVA treatment leads to clinically meaningful improvements in lung function, but also suggest that ELX/TEZ/IVA can have an impact on lung function even in those patients with CF who have well-conserved pulmonary status according to spirometry.

Consistent with the improvements in lung function observed over the course of the study period, participants also had declines in the number of PEx. The occurrence of PEx in people with CF contributes to both overall declines in lung function over time as well as increased incidence of antibiotic usage and/or hospitalizations. Prior to initiation of ELX/TEZ/IVA, participants experienced an average of 1.3 PEx per year. Following initiation of ELX/TEZ/IVA, the overall annual rate of PEx declined by 53%, with similar declines seen in rates of PEx requiring intravenous antibiotics or hospitalizations.

Beyond changes in pulmonary function, participants in the current study also had improvements in nutritional parameters and HbA1c. BMI and BMI z-score increased early following ELX/TEZ/IVA initiation and improvements were sustained through 12 months. These results are consistent with those reported in the pivotal clinical trials of ELX/TEZ/IVA and their extension studies. CF-related diabetes is a complication of CF disease resulting from abnormal glucose metabolism caused by insulin deficiency. The incidence of CF-related diabetes has been shown to increase with age and CF disease progression, with 2% of children, 19% of adolescents, and up to 50% of adults reportedly having been diagnosed with CF-related diabetes [18]. In the current study, mean HbA1c was 6.07% at baseline, a level considered to be suggestive of pre-diabetes, with a range of 4.40%–18.80%. At 6 months after initiation of ELX/TEZ/IVA, mean HbA1c had decreased to 5.92% (absolute change of −0.3) with a range of 4.50%–13.80%. Decreases of 0.30% in HbA1c are considered clinically meaningful to reduce diabetic complications [19]. In a community-based study of nondiabetic adults, it was found that HbA1c was strongly associated with the likelihood of developing diabetes as well as risk for cardiovascular disease and death from all causes [20]. Notably, the decline in HbA1c observed in this study at 6 months was generally sustained through the remainder of the follow-up period, suggesting that treatment with ELX/TEZ/IVA could potentially be associated with early and maintained improvements in glucose metabolism in people with CF. The decrease in HbA1c may indicate a decrease in the relative risk for diabetic diagnosis and coronary heart disease. However, further studies will be required to fully understand the potential impacts of ELX/TEZ/IVA treatment on insulin secretion and glucose metabolism in people with CF.

There are some limitations to the current study that should be considered. First, because this was an observational, single-arm study without a comparator group, study results should be interpreted carefully. Second, this study included 15 sites, which may have data variability across EMRs since there is no data standardization. Data are limited to what is captured in the EMRs, with data collected by individuals providing care rather than curation of data for research. Next, the post-ELX/TEZ/IVA treatment period of this study overlapped with the SARS-CoV-2 pandemic. Most study participants (75%) initiated ELX/TEZ/IVA prior to March 2020 and 87% of their follow-up period occurred during the pandemic. Global masking and social distancing measures may have led to decreases in the incidence of PEx due to reduced exposure to respiratory viral infections [21]. Given that people with CF were considered at higher risk

for SARS-CoV-2, different care delivery methods were implemented to reduce transmission (i.e., reduction of in-person clinic visits and increased remote monitoring and telemedicine visits). Data in the EMR may have been impacted by gaps in care or care delivery. Patel et al. found that SARS-CoV-2 restrictions were associated with decreased PEx events in younger children with CF (aged 2–12 years) and a shift toward PEx diagnosis through telephone encounters rather than in-person visits [21], which could have impacted the background rate of PEx.

5. Conclusions

Here, we show that people with CF taking ELX/TEZ/IVA in real-world settings had improvements in lung function, reductions in the frequency of PEx, increases in BMI and BMI z-scores, and improved HbA1c levels that were seen early and maintained during a 16-month follow-up period. These results confirm the broad clinical benefits of ELX/TEZ/IVA treatment previously reported in pivotal clinical trials and show the potential for ELX/TEZ/IVA to improve markers of diabetes.

Ethical statement

The study protocol, amendments, and other necessary documents were reviewed and approved by an IRB for each of the 15 integrated health systems before initiation of the study at that site. The study was being conducted in compliance with the US FDA Title 21 CFR Part 50 – Protection of Human Patients and Part 56 – IRBs; the International Council for Harmonization for Pharmaceuticals for Human Use Good Clinical Practice guidelines E6(R2) (November 9, 2016) as they apply to post-marketing, observational studies; the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology; the Belmont Report; US Title 45 CFR Part 164 Subpart E – Privacy of Individually Identifiable Health Information and the Health Insurance Portability and Accountability Act of 1996 Privacy Rule (2002); and any applicable national guidelines. A waiver of informed consent was requested from IRBs. As their data in the analytic file was de identified, no patient or caregiver consent was required.

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Data availability

Vertex Pharmaceuticals Incorporated is committed to advancing medical science and improving patient health. This commitment includes the responsible sharing of clinical study data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex Pharmaceuticals Incorporated 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.

CRediT authorship contribution statement

Thomas Keens: Writing – review & editing, Formal analysis, Conceptualization. **Veena Hoffman:** Writing – review & editing, Formal analysis, Conceptualization. **Ia Topuria:** Writing – review & editing, Formal analysis, Conceptualization. **Ken Elder:** Writing – review & editing, Formal analysis, Conceptualization. **Shannon Cerf:** Writing – review & editing, Formal analysis, Conceptualization. **Kyra Mulder:** Writing – review & editing, Formal analysis, Conceptualization. **Jon Roberts:** Writing – review & editing, Formal analysis, Conceptualization. **Jerimiah Lysinger:** Writing – review & editing, Formal analysis, Conceptualization. **Maria Del Carmen Reyes:** Writing – review & editing, Formal analysis, Conceptualization. **Maria Berdella:** Writing – review & editing, Formal analysis, Conceptualization. **Anne Marie Cairns:** Writing – review & editing, Formal analysis, Conceptualization. **Manu Jain:** Writing – review & editing, Formal analysis, Conceptualization. **Vaidyanathan Ganapathy:** Writing – review & editing, Formal analysis, Conceptualization. **Yiyue Lou:** Writing – review & editing, Formal analysis, Conceptualization. **Bassem Morcos:** Writing – review & editing, Formal analysis, Conceptualization. **Chuntao Wu:** Writing – review & editing, Formal analysis, Conceptualization. **Laura Sass:** Writing – review & editing, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All Authors report writing assistance was provided by Vertex Pharmaceuticals Incorporated. Laura Sass reports a relationship with Girl Scout Council of the Colonial Coast that includes: board membership. Yiyue Lou reports a relationship with Vertex that includes: employment. Bassem Morcos reports a relationship with Vertex Pharmaceuticals Incorporated that includes: employment. Chuntao Wu reports a relationship with Vertex Pharmaceuticals Incorporated that includes: employment. Shannon Cerf reports a relationship with OM1 Inc that includes: employment. Kyra Mulder reports a relationship with OM1 Inc that includes: employment. Veena Hoffman reports a relationship with OM1 Inc that includes: employment. Jerimiah Lysinger reports a relationship with Rocky

Mountain Chapter of the CFF that includes: board membership. Chuntao Wu reports a relationship with Alexion Pharmaceuticals Inc that includes: equity or stocks. Chuntao Wu reports a relationship with Sanofi that includes: equity or stocks. Manu Jain reports a relationship with Vertex Pharmaceuticals Incorporated that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28508.

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