ABSTRACT

Title	Real-World Effects and Utilisation Patterns of Elexacaftor, Tezacaftor, and Ivacaftor Combination Therapy (ELX/TEZ/IVA) in Patients with Cystic Fibrosis (CF) Date of the abstract: 04 December 2025 Author: Vertex Pharmaceuticals Incorporated, USA
Keywords	Elexacaftor/Tezacaftor/Ivacaftor, Cystic Fibrosis, Long-term Safety, Disease Progression, Drug Utilisation
Rationale and Background	CF is an autosomal recessive disease with serious and chronically debilitating morbidities, as well as high premature mortality. ELX/TEZ/IVA combination therapy is a *CFTR* corrector / potentiator combination that targets the underlying cause of CF and is intended for chronic and potentially lifelong use. This 5-year observational post-authorisation safety study (PASS) evaluated safety, disease progression, and pregnancy outcomes in patients with CF who were treated with ELX/TEZ/IVA, and also described drug utilisation patterns under the real-world conditions of use.
Research Question and Objectives	**Primary Objectives:** 1. Evaluate safety outcomes (i.e., death, organ transplant, hospitalisation, pulmonary exacerbations [PEx], CF complications, respiratory microbiology, liver function tests [LFTs], and other events of interest) in patients treated with ELX/TEZ/IVA in the real-world setting. 2. Evaluate effectiveness outcomes / CF disease progression (i.e., changes over time in lung function and nutritional status) in patients treated with ELX/TEZ/IVA in the real-world setting. 3. Evaluate safety and effectiveness outcomes / CF disease progression in genotype subgroups (including *F508del* homozygous [F/F], *F508del*/minimal function [F/MF], *F508del*/residual function [F/RF], and *F508del*/gating [F/G]). 4. Evaluate the frequency and outcome of pregnancy in female patients treated with ELX/TEZ/IVA in the real-world setting. 5. Describe drug utilisation patterns and characterise potential off-label use of ELX/TEZ/IVA in patients outside of the labelled indication.
Study Design	This 5-year observational cohort study used data from patients treated with ELX/TEZ/IVA as collected by CF patient registries in the US (CF Foundation Patient Registry [CFFPR]) and Germany (German CF Registry) (all study objectives), as well as from the European CF Society Patient Registry (ECFSPR) (drug utilisation; Objective 5 only). In the US CFFPR and German CF Registry, within-cohort evaluation of outcomes in the 5-year periods before and after treatment initiation were performed. Evaluation of the outcome patterns and trends in the 5-year pre-treatment period placed into context the outcome patterns and trends observed in the post-treatment period.
Setting / Data Sources	For all study objectives, data from the US CFFPR and German CF Registry allowed for characterisation of longitudinal patterns in a broad range of safety and effectiveness / CF disease progression outcomes within large cohorts of ELX/TEZ/IVA-treated patients in the US and EU. In addition, the ECFSPR was used to provide additional information for the evaluation of drug utilisation patterns in the European region (Objective 5).
Population	Patients included in the existing CF patient registries participating in the study were the source population for all study analyses. To address the study objectives, the following cohorts were established in these registries:

Longitudinal Safety and Effectiveness / CF Disease Progression Analyses Cohorts (established separately in US CFFPR and German CF Registry)

These cohorts (referred hereafter as ELX/TEZ/IVA Cohorts) included all patients who had a first record of treatment with ELX/TEZ/IVA in each registry during the cohort eligibility period, regardless of age and genotype.

ELX/TEZ/IVA Cohorts were followed over the course of study (through 2024), up to 5 years. For each of the follow-up years, only patients remaining on treatment from the previous year were included in analyses.

Pregnancy Analyses Cohorts (established separately in US CFFPR and German CF Registry)

These cohorts were subsets of the ELX/TEZ/IVA Cohorts and included all female patients aged 14 years and older. The US CFFPR limited this cohort to ages ≥14 to 45 years.

Drug Utilisation Analyses Cohorts (established separately in the US CFFPR, German CF Registry, and ECFSPR)

These cohorts included all patients in the registries with a record of ELX/TEZ/IVA use at any time during each of the analysis years. In addition, the ECFSPR was used to provide additional information to evaluate drug utilisation patterns in the European region.

Study Size

This final analysis covers the period through 31 December 2024. The cohort sizes throughout the study period are summarised below.

Study Cohort	Analysis Year	1	2	3	4	5	Cumulative
	Cohort Size	N					Person-years or Count [a, b]
ELX/TEZ/IVA Cohort	US	16,104	13,105	11,854	10,838	9,885	57,254.84
	Germany	2,858	2,754	2,585	2,464	1,332	10,111.58
Pregnancy Cohort [b]	US	6,155[c]	5,933	5,002	4,596	4,180	6,629
	Germany	-	1,255	1,237	1,206	1,160	1,371
Drug Utilisation Cohort [b]	US	16,254	21,058	22,185	24,903	25,832	N/A
	Germany	923	3,209	4,263	4,728	5,391	
	ECSPR	5,373	15,735	25,612	30,442	34,660	

ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; US: United States; ECFSPR: European Cystic Fibrosis Society Patient Registry

[a] Total N for cmulative pregnancy cohort includes a subset of patients eligible to be in pregnancy cohort in each year of analysis and at any time during the full follow-up period.

[b] Cohorts are analysed cross-sectionally, per study protocol. For these outcomes, analyses are conducted on the calendar year basis (versus ELX/TEZ/IVA exposure year).

[c] In Year 1 in the US, cohort included all those eligible for pregnancy analyses in 2019 or 2020 (cumulative analysis covered 2020 through 2024).

Variables

All study variables (exposure, safety endpoints, disease progression outcomes, pregnancy variables, drug utilisation outcomes, and other key variables) were collected by the registries in pre-specified data collection forms, according to established data entry guidelines.

Exposure

- ELX/TEZ/IVA exposure as recorded in the registries

Outcomes

Safety

- Death, organ transplant, hospitalisations, PEx
- CF complications
- Respiratory microbiology
- LFTs

Effectiveness / CF Disease Progression

- $ppFEV_1$
- BMI

Pregnancy

- Pregnancy outcome (live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown)
- Congenital anomalies of pregnancy outcome (as available)

Drug Utilisation

- ELX/TEZ/IVA use outside of the labelled indication
- ELX/TEZ/IVA use within the labelled indication

Other Key Variables

- Age at the initiation of ELX/TEZ/IVA
- Gender
- Genotype
- Baseline $ppFEV_1$
- Baseline moderate or severe hepatic impairment status
- Organ transplant history
- History of other CFTR modulator use/exposure
- CF medications

Results

The Final Analysis of the ELX/TEZ/IVA PASS identified no new safety concerns and showed consistent favourable patterns in key disease progression outcomes based on analyses of US CFFPR and German CF Registry data through 31 December 2024.

Safety and Disease Progression Analyses Results

16,104 patients started ELX/TEZ/IVA and were included in US analyses. These patients accrued a mean (SD) of 42.3 (22.2) months of follow-up as of 31 December 2024. In Germany, 2,858 CF patients initiated ELX/TEZ/IVA. These patients accrued a mean (SD) exposure duration of 42.5 (12.5) months of follow-up as of 31 December 2024.

In this final report, patterns in key evaluated safety and disease progression outcomes following treatment initiation across two independent registries were consistent with a favourable benefit-risk profile for ELX/TEZ/IVA, and no new safety concerns were identified:

- Rates of death and organ transplantation (including lung transplantation) during the post-treatment period were considerably lower than historically reported in both the US and in Germany among people with CF.
- Frequencies of hospitalisations and PEx in both the US and in Germany decreased in the post-treatment period compared to the pre-treatment period and remained low through the duration of follow-up to date. Supplementary analyses in the subsets of patients with available 5-year pre-treatment data were consistent with these favourable trends.
- Mean $ppFEV_1$ increased in the post-treatment period in both the US and in Germany compared to the baseline Year -1 among patients with available lung function data before and after treatment initiation. Findings were similar in supplementary analyses performed in a subset of patients who had non-missing lung function data in each of the five pre-treatment years and post-treatment years. In these analyses, an increase in mean $ppFEV_1$ following treatment initiation was observed after a consistent pattern of

a decline in lung function in the 5-year pre-treatment period in the overall study population.

- Mean body mass index (BMI) increased following treatment initiation in both registries; supplementary analyses in a subset of patients with available 5-year pre-treatment data and post-treatment data showed that increases in BMI over time were also observed during the pre-treatment period.
- The prevalence of all evaluated pathogens (with the exception of *Haemophilus influenzae* in both registries and *Klebsiella* in Germany) declined and continued to be lower in the post-treatment period compared to the baseline Year -1, as reported in previous interim analyses (IAs). Findings were similar in supplementary analyses performed in a subset of patients who had non-missing bacterial culture data in each of the five pre-treatment years and post-treatment period.
- Prevalence estimates for specific types of CF complications in the post-treatment period were generally comparable (with overlapping 95% CIs) to the pre-treatment Year -1 or consistent with CF disease progression patterns observed in the 5-year pre-treatment period in both registries, indicating no new safety concerns. In the small subgroup with available patient health questionnaire (PHQ-9) data in Germany, PHQ-9 scores in the post-treatment period were generally comparable to the calendar year prior to treatment initiation (Year -1).
- Among patients with available LFT results, the proportion of patients with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations above 3, 5, or 8 times the upper limit of normal (ULN) were generally comparable in the post-treatment period to the pre-treatment period in both registries, and frequency of BILI elevations above 2 times the ULN was higher post-treatment consistent with the clinical study results and the product label. Findings were similar in the supplementary analyses performed in a subset of patients who had non-missing LFT data in each of the five pre-treatment years.
- For all safety and effectiveness / disease progression outcomes in both US and Germany registries, patterns observed in the overall cohort were consistent in genotype subgroups where there was sufficient sample size available.

Overall, during the study follow-up through 31 December 2024, 16.4% in the US ELX/TEZ/IVA Cohort and 9.9% in the Germany ELX/TEZ/IVA Cohort met the study definition of treatment discontinuation.

Pregnancy Analyses Results

- Pregnancy frequency in 2024 among female patients aged ≥14 to 45 years in the US in 2023 was 7.8%. Pregnancy frequency among female patients aged ≥14 years in Germany in 2024 was 2.9%. Over the full study period, annual pregnancy frequency ranged from 7.4% to 8.7% in the US and 3.9% to 5.4% in Germany.
- The distribution of pregnancy outcomes did not indicate any safety concerns in either the US CFFPR or Germany CF Registry analyses in 2024 or in the cumulative pregnancy analysis.

Drug Utilisation Analyses Results

- The annual number of patients exposed to ELX/TEZ/IVA increased over time from 2020 to 2024, from 16,254 to 25,832 in the US, 923 to 5,391 in Germany, and 5,373 to 34,660 in ECFSPR.
- Analyses of drug utilisation patterns in the US CFFPR, German CF Registry, and ECFSPR showed that prevalence of off-label use over the full study period was generally low (≤2%, <5%, and ≤7% in all years, respectively).

Discussion	The results of this final analysis of data from the US CFFPR, German CF Registry, and ECFSPR did not identify new safety concerns in ELX/TEZ/IVA-treated patients based on evaluation of safety and disease progression outcomes. Information from patients on pregnancy and potential off-label use did not identify any new safety concerns. Consistent favourable findings were observed in key disease progression outcomes. Safety and effectiveness findings were consistent with the current understanding of the ELX/TEZ/IVA benefit-risk profile.