ABSTRACT

Title	Utilisation Patterns and Real-World Effects of Tezacaftor and Ivacaftor Combination Therapy (TEZ/IVA) in Patients With Cystic Fibrosis (CF) Date of the abstract: 02 December 2022 Author: Vertex Pharmaceuticals Incorporated
Keywords	Tezacaftor/Ivacaftor, Cystic Fibrosis, Long-term Safety, Disease Progression, Drug Utilisation
Rationale and Background	Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities, and high premature mortality. Tezacaftor (TEZ) and ivacaftor (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 observational post-authorisation safety study (PASS) evaluated safety, disease progression, and pregnancy outcomes in patients with CF who were treated with TEZ/IVA, as well as described drug utilisation patterns under the real-world conditions of use.
Research Question and Objectives	Primary Objectives: 1. To evaluate safety outcomes in patients with CF who have mutations that are indicated for TEZ/IVA, and are treated with TEZ/IVA in the real-world setting (i.e., death, organ transplant, hospitalisation, pulmonary exacerbations (PEx), CF complications, pulmonary pathogens, and liver function test results [LFTs]) 2. To evaluate CF disease progression in patients who have mutations that are indicated for TEZ/IVA, and are treated with TEZ/IVA in the real-world setting, as measured by changes over time in lung function (percent predicted forced expiratory volume in 1 second [$ppFEV_1$]) and nutritional status (body mass index [BMI]) 3. To evaluate the frequency and outcome of pregnancies in female patients who are 14 years of age and older, have mutations that are indicated for TEZ/IVA, and are treated with TEZ/IVA 4. To evaluate drug utilisation and characterise potential off-label use of TEZ/IVA in patients outside the labelled indication (e.g., patients who do not have mutations that are indicated for TEZ/IVA)
Study Design	This was an observational cohort study using data collected by national CF patient registries. Primary analyses focused on within-cohort evaluation of outcomes in the pre- and post-treatment initiation periods.

Subjects and Study Size

This report covers the period through 31 December 2021 and focuses on evaluation of US Cystic Fibrosis Foundation Patient Registry (CFFPR) data, the German CF Registry, and the UK CF Registry data for all study objectives, as well as data from Ireland and France for the drug utilisation objective.

The following table summarises the cohort sizes that are the focus of analyses presented in this report.

Study Cohort		Analysis Year				
	Cohort Size	Year 1	Year 2	Year 3	Year 4	Cumulative[a,b]
		N				Person-years
TEZ/IVA 12+ Cohort	**US**	4,489	3,551	353	118	6252.99
	Germany	610	525	154	-	871.72
	UK	1,697	373	-	-	1,317.05
TEZ/IVA 6-11 Cohort	**US**	532	402	120	-	799.35
	Germany	38	-	-	-	N/A
	UK	201	-	-	-	N/A
Pregnancy Cohort[a]	**US**	2,167	1,837	184	55	2,245
	Germany	306	274	82	-	318
	UK	688	161	-	-	689
Drug Utilisation Cohort	**US**	4,663	6,854	2,766	1,562	N/A
	Germany	822	987	425	-	
	UK	22	2,904	1,078	-	
	Ireland	150	157	72	-	
	France	203	-	-	-	

TEZ/IVA: tezacaftor in combination with ivacaftor; UK: United Kingdom; US: United States
Note: The TEZ/IVA 12+ Cohorts included patients aged ≥12 year at treatment initiation. The TEZ/IVA 6-11 Cohort included patients aged 6 through 11 years at treatment initiation.
[a] Total N for Cumulative pregnancy cohort includes a subset of 12+ Cohort patients eligible to be in pregnancy cohort in each year of analysis in addition to a subset of the 6-11 Cohort patients who turn 14 years of age or older in the study follow-up years.
[b] Drug Utilisation Cohorts are analysed cross-sectionally, per study protocol.

Variables and Data Sources

For this report, 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. The study variables are summarised in the table below.

Category	Variable
Exposure	• TEZ/IVA exposure as recorded in the respective registries
Safety analyses endpoints	• Death, organ transplant, hospitalisations, pulmonary exacerbations • CF complications • Pulmonary pathogens • LFTs
Disease progression analyses endpoints	• $ppFEV_1$ • BMI
Pregnancy analyses endpoints	• Pregnancy outcome (live birth, stillbirth, spontaneous or therapeutic abortion, undelivered, and unknown)
Drug utilisation analyses endpoints	• TEZ/IVA use outside the labelled indications • TEZ/IVA use within any expanded label indications
Other key variables (part of descriptive analyses and / or stratification variables)	• Age, gender, genotype • $ppFEV_1$ • History of moderate or severe hepatic impairment • Organ transplant history

	• TEZ/IVA exposure duration • History of CFTR modulator use/exposure • CF medications
Results	No new safety concerns were identified based on analyses of US CFFPR, German CF Registry, and UK CF Registry data through 31 December 2021. Overall, safety and disease progression outcome patterns were evaluated for up to 4 years of TEZ/IVA exposure in the US, up to 3 years of TEZ/IVA exposure in Germany and up to 2 years in the UK, with all results consistent over time and across these large independent patient registries. <u>Safety and Disease Progression Analyses Results</u> Safety and disease progression outcomes were evaluated for the US 12+ Cohort (up to 4 years of exposure, 6252.99 person-years), Germany 12+ Cohort (up to 3 years of exposure, 871.72person-years), UK 12+ Cohort (up to 2 years of exposure, 1,317.1 person-years), US 6-11 Cohort (up to 3 years of exposure, 799.35 person-years), and Germany and UK 6-11 Cohorts (1st year of exposure each). The sizes of US, Germany, and UK 12+ Cohorts, and US 6-11 Cohort declined significantly over time reflecting the declining real-world utilisation of TEZ/IVA following approval of novel CFTR modulator elexacaftor (ELX)/TEZ/IVA. As such, only 118 of 4,489 (2.6%) patients in the initial US 12+ Cohort remained on therapy in the fourth year; only 154 of 610 (25.2%) patients in the initial Germany 12+ Cohort remained on therapy in the third year; only 373 of 1,697 (22.2%) patients in the initial UK 12+ Cohort remained on therapy in the second year; and only 120 of 532 (22.6%) patients in the initial US 6-11 Cohort remained on therapy in the third year. The primary reason for the patient attrition from all the cohorts was switching to another CFTR modulator (e.g., ELX/TEZ/IVA). Despite the evolution of the cohorts due to patient attrition, the primary and supplementary analyses across all 3 registries (US, Germany, UK) and all cohorts (12+, 6-11) showed that the patterns of the key evaluated safety and disease progression outcomes following treatment initiation were consistent with the benefit-risk profile of TEZ/IVA, with no new safety concerns identified: • *Deaths and transplantations* Across all registries, and in each of the follow-up years, risks of death and transplantation were low. The cumulative rates of death and organ transplantation in the 12+ Cohorts were lower or similar in this study as compared to the rates seen historically (before TEZ/IVA availability) in the broader CF patient populations. There were no deaths or organ transplants in the 6-11 Cohorts in any of the 3 registries in the study. • *Pulmonary exacerbations and hospitalisations* Across all registries, and in both, 12+ and 6-11 Cohorts, cumulative rates of hospitalisations and PEx per person-year of TEZ/IVA exposure were less than pre-treatment baseline year and frequencies of hospitalisation and PEx continued to decline in the post-treatment initiation period compared to the pre-treatment period. Supplementary analyses in subsets of patients with available 5-year pre-treatment data were consistent with these favourable trends. • *Lung function* Across all registries, and in both, 12+ and 6-11 Cohorts, mean ppFEV$_1$ increased numerically post-treatment initiation among patients with available data. This pattern was in contrast to the progressive loss of lung function over time observed during the pre-treatment period in 12+ Cohorts in the supplementary analyses in subsets of patients with available 5-year pre-treatment data. • *BMI* Across all registries, and in both 12+ and 6-11 Cohorts, mean BMI increased numerically following treatment initiation; supplementary analyses in a subset of

	patients with available 5-year pre-treatment data showed that increases in BMI over time were also observed during the pre-treatment period. • *CF complications* Across all registries, and in both 12+ and 6-11 Cohorts, prevalence of evaluated complications post-treatment initiation was generally comparable to the pre-treatment period. None of the evaluated complications indicated a new safety concern. Supplementary analyses in a subset of patients with available 5-year pre-treatment data were generally consistent with overall results, with greater variability due to small sample sizes. • *Bacterial pathogens* Across all registries, and in both 12+ and 6-11 Cohorts, among patients with available bacterial culture data, the prevalence of evaluated pathogens was generally similar or lower numerically in the post-treatment initiation period as compared to the pre-treatment period. None of the evaluated pathogens indicated a new safety concern. • *LFT elevations* Across all registries, among patients with available LFT results in both 12+ and 6-11 Cohorts, the frequency of LFT elevations was generally comparable in the post-treatment initiation period and the pre-treatment period. Evaluation of LFT abnormalities did not indicate a new safety concern. <u>Pregnancy Analyses Results</u> Cumulatively, there were 155/2,245 (6.9%) pregnancies in the US, 10/318 (3.1%) pregnancies in Germany and 36/689 (5.2%) pregnancies in the UK cohorts of females older than 14 years of age and treated with TEZ/IVA during this study. Across all 3 registries, the frequency of the outcomes of pregnancies (still birth, spontaneous abortion, therapeutic abortion) among female patients treated with TEZ/IVA were generally similar to what is observed in the general population and / or untreated CF populations. No safety concerns were identified. <u>Drug Utilisation Analyses Results</u> Analyses of drug utilisation patterns over the course of the study showed a declining utilisation of TEZ/IVA with a relatively low prevalence of potential off-label use across all regions (1.7% in the US, 6.4% in Germany, 12.2% in the UK, 2.8% in Ireland, and 6.4% in France in 2021). The primary reason for potential off-label use across the registries was use in patients without indicated genotypes.
Discussion	Overall, the results of the analyses of data from 3 large, independent registries were consistent with the current understanding of the benefit-risk profile of TEZ/IVA, with no new safety concerns identified. Given the continued favorable findings, and a significant decline in the real-world utilisation of TEZ/IVA resulting in diminishing cohort sizes impacting the ability to perform meaningful analyses in the future, this report is proposed to be the final report for the TEZ/IVA PASS.
Marketing Authorisation Holder(s)	Vertex Pharmaceuticals (Ireland) Ltd.