Post-Authorisation Safety Study Information

VERTEX PHARMACEUTICALS INCORPORATED

Title	Utilisation Patterns and Real-World Effects of Tezacaftor and Ivacaftor Combination Therapy (TEZ/IVA) in Patients With Cystic Fibrosis (CF)
Version identifier	Version 2.0
Date	06 March 2019
EU PAS Register Number	Study will be registered in the EU PAS Register following PRAC approval of the final protocol, and before study initiation.
Active Substance	Tezacaftor (VX-661) and ivacaftor (VX-770)
Medicinal Product	Symkevi
Product Reference	EMEA/H/C/004682
Procedure Number	N/A
Marketing Authorisation Holder(s)	Vertex Pharmaceuticals (Europe) Ltd.
Joint PASS	No
Research Questions and Objectives	Primary Objectives: 1. To evaluate safety outcomes in patients with CF who have mutations indicated for TEZ/IVA, and are treated with TEZ/IVA in the real world setting (i.e., death, organ transplant, hospitalisation, pulmonary exacerbations, CF complications, respiratory microbiology, 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 and older, have mutations that are indicated for TEZ/IVA, and are treated with TEZ/IVA 4. To evaluate the drug utilisation and to 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)
Country(-ies) of Study	United States (US), Germany, United Kingdom (UK), Ireland, and France
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BILI	bilirubin
BMI	body mass index
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFRD	cystic fibrosis-related diabetes
CFRI	Cystic Fibrosis Registry of Ireland
CFT	Cystic Fibrosis Trust
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CI	confidence interval
CRA	Clinical Research Associate
CYP	cytochrome P450
DIOS	distal intestinal obstruction syndrome
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union Post-authorisation Study
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
GI	gastrointestinal
GLI	Global Lung Initiative
ICF	informed consent form
IRB	institutional review board
IV	intravenous
IVA	ivacaftor
LUM/IVA	lumacaftor in combination with ivacaftor
LFT	liver function test
max	maximum value
min	minimum value
MRSA	methicillin-resistant *Staphylococcus aureus*
PASS	post-authorisation safety study
PEx	pulmonary exacerbation
PRAC	Pharmacovigilance Risk Assessment Committee
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
RF	residual function
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
TEZ	tezacaftor
TEZ/IVA	tezacaftor in combination with ivacaftor

Abbreviation	Definition
UK	United Kingdom
ULN	upper limit of normal
US(A)	United States (of America)

3 RESPONSIBLE PARTIES

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4 ABSTRACT

Title	Utilisation Patterns and Real-World Effects of Tezacaftor and Ivacaftor Combination Therapy in Patients With Cystic Fibrosis
Phase	Post-authorisation safety study (PASS)
Rationale and Background	Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities, and high premature mortality. CF affects approximately 70,000 individuals worldwide and is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*), which results in the absence or deficient function of the CF transmembrane conductance regulator (CFTR) protein at the cell surface. Tezacaftor (TEZ) and ivacaftor (IVA) combination therapy is currently indicated for treatment of CF in patients 12 years and older who have specified *CFTR* mutations and is intended for chronic and potentially lifelong use. In both the EU and the US, the indicated population includes patients who have two copies of the *F508del* mutation. Additionally in the European Union (EU), TEZ/IVA is indicated for patients heterozygous for the *F508del* mutation and one of 14 mutations in which the CFTR protein shows residual activity (referred hereafter as residual function [RF] mutations); in the United Stated (US) TEZ/IVA is also indicated for patients with at least one copy of 26 RF mutations. The list of indicated mutations, by region, is provided in Annex 3. In Phase 3 studies, a clinically meaningful benefit in patients homozygous for *F508del* and patients heterozygous for *F508del* and a residual function mutation was demonstrated across multiple endpoints addressing the key primary goals of CF treatment: improving lung function, reducing pulmonary exacerbations, enhancing nutritional status, and improving quality of life (respiratory symptoms). TEZ/IVA was generally well tolerated, and no unique safety concerns attributable to TEZ/IVA were identified. The favorable benefit-risk profile makes TEZ/IVA an important therapy for the populations covered by the indication. Information regarding the safety profile of the therapy under the real-world conditions of use will be informative to patients, caregivers, prescribers, and payers. Existing CF registries provide an established source to obtain these data.
Research Questions 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, 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 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 is a 5 year observational cohort study using data collected by CF patient registries in US, Germany, and UK (all study objectives), as well as Ireland and France (drug utilisation objective only) for patients treated with TEZ/IVA. Within-cohort evaluation of outcomes in the pre- and post-treatment periods will be performed (US, Germany, UK). Certain conditions may warrant early study termination (e.g., significant proportion of

patients discontinuing TEZ/IVA due to availability of novel CFTR modulators).

Study Population

Patients included in the existing CF patient registries participating in the study are the source population for all study analyses. To address the study objectives, the following cohorts will be established in these registries.

Longitudinal safety and disease progression analyses cohorts (established separately in US, German and UK registries)

These cohorts (referred hereafter as TEZ/IVA Cohorts) will include all patients who have a first record of treatment with TEZ/IVA in the registry during cohort eligibility period, are aged 12 years and older, and have indicated mutations (Annex 3). The cohort eligibility period will be defined as the first calendar year of commercial availability of TEZ/IVA in the respective country; however if during the first year of commercialisation the uptake of TEZ/IVA is slower / lower than expected, the cohort eligibility period may be extended by one year. Additionally, if it is determined over the course of the study that there are large patient populations of new users who are systematically different from the patients who initiated TEZ/IVA during the cohort eligibility period (e.g., indication expanded to patients ≤12), additional separate cohorts may be established for safety and disease progression analyses.

TEZ/IVA Cohorts will be followed over the course of study duration (2018 through 2022), up to 5 years. For each of the follow-up years, only patients remaining on treatment from the previous year will be included.

Pregnancy analyses cohorts (established separately in US, German and UK registries)

These cohorts are sub-sets of TEZ/IVA Cohorts including all female patients aged 14 years and older.

Drug utilisation analyses cohorts

These cohorts will include all patients in the registries with record of TEZ/IVA use at any time during each of the analysis years. In addition to US, German, and UK registries, Drug Utilisation Cohorts will be established in the CF registries of Ireland and France.

Variables

Exposure

- TEZ/IVA exposure as recorded in the registries

Endpoints

Analyses	Endpoints
Safety	• Death, organ transplant, hospitalisations, pulmonary exacerbations • CF complications • Pulmonary pathogens • LFTs
Disease progression	• $ppFEV_1$ • BMI
Pregnancy	• Pregnancy outcome (live birth, stillbirth, spontaneous or therapeutic abortion, undelivered, and unknown) • Gestational age, congenital anomalies (if available)
Drug utilisation	• TEZ/IVA use outside the labeled indications • TEZ/IVA use within any expanded label indications

Covariates

- Age, sex, genotype
- $ppFEV_1$

	• Moderate or severe hepatic impairment • Organ transplant history • TEZ/IVA exposure duration • History of CFTR modulator use/exposure • CF medications
Data Sources	Data sources will include: • US CF Foundation Patient Registry (all study objectives) • German CF Registry (all study objectives) • UK CF Registry (all study objectives) • CF Registry of Ireland (drug utilisation objective) • CF Registry of France (drug utilisation objective)
Study Size	Study size will depend on the patterns of use of TEZ/IVA in routine clinical practice. Based on 2017 data, the US CF Foundation registry (largest to be evaluated in this study) had a total of 8,111 patients homozygous for *F508del* aged 12 years or older, and 1,512 patients with one of 26 residual function mutations indicated in the US aged 12 years and older (of them, a sub-set of 958 patients had RF genotypes indicated in EU). However, the size of TEZ/IVA treated population can be expected to be smaller, reflecting the real-world uptake and availability of alternative CFTR modulators for these patient populations (e.g., lumacaftor and ivacaftor in combination (LUM/IVA) for patients homozygous for *F508del*; IVA in the US for patients with responsive RF mutations). The size of the population eligible for TEZ/IVA treatment in Germany and the UK is expected to be significantly smaller than in the US CF Foundation registry based on the differences in CF population size, as well as indicated genotypes in Europe versus the US.
Data Analysis	To meet the study objectives, data will be analysed separately for each registry over the course of the 5 year study (2018 through 2022). The results of the analyses will be presented in the annual study reports. Each annual report will include the patient data collected through the end of the previous calendar year. Descriptive statistics will be presented for all study endpoints. Continuous variables will be summarized using the following descriptive summary statistics where appropriate: the number of observations (n), mean, standard deviation (SD), standard error (SE), 95% confidence intervals (CI), median, minimum value (min), and maximum value (max). Categorical variables will be summarized using counts, percentages and 95% CIs as appropriate. All safety and CF disease progression endpoints (Objectives 1 and 2, respectively) and pregnancy endpoints (Objective 3) will be evaluated in the TEZ/IVA Cohorts in the US, German, and UK registries. **Study periods** For safety outcomes and disease progression analyses within the TEZ/IVA Cohorts in each registry, pre-treatment and post-treatment periods will be defined as described below. The definition of the periods will vary depending on whether the registry employs encounter-based data collection which allows for anchoring the periods on the date of TEZ/IVA treatment initiation (US), or uses annual data collection which necessitates analyses based on the calendar years (Germany and UK). • **Pre-treatment period** will be defined in the encounter-based US registry as the 5 years before the date of TEZ/IVA treatment initiation (index date). In the German and UK registries, this period will be defined as the 5 calendar years before the cohort eligibility period.

- Within the pre-treatment period, the 12 months immediately preceding TEZ/IVA treatment initiation date (US) or the calendar year immediately preceding the cohort eligibility period (Germany and UK) will be considered as **pre-treatment baseline** for all analyses of change from baseline.

- **Post-treatment period** in the encounter-based US registry will continue for up to 5 years after TEZ/IVA treatment initiation. In German and UK registries this period will continue for up to 5 calendar years from commercialisation.

Safety outcome analyses

Annualized risks of death, organ transplant, hospitalisations, and pulmonary exacerbations will be calculated for each year of the post-treatment period, and for the pre-treatment baseline year where appropriate.

Similarly, prevalence of CF complications, frequency of pulmonary pathogens, as well as proportions of patients with abnormal LFT results will be calculated for each year of the post-treatment period, and for the pre-treatment baseline year.

Analyses of all safety outcomes will be stratified by patient genotype, sex, age at TEZ/IVA treatment initiation, baseline $ppFEV_1$, prior history of CFTR modulator use, and other variables as appropriate (e.g., moderate to severe hepatic impairment, organ transplant history).

Additional in-depth analyses may be performed for outcomes deserving further investigation if sufficient data are available.

Supplementary descriptive analyses of safety outcomes in the 5 year pre-treatment period may be performed to provide additional context to trends observed during the post-treatment period, if retrospective data are available

Disease progression analyses

The evaluation of CF disease progression will be based on assessment of change from the pre-treatment baseline year over time in lung function and BMI in the TEZ/IVA Cohorts. Analyses may be stratified by patient genotype, age at TEZ/IVA treatment initiation, baseline $ppFEV_1$ and prior history of CFTR modulator use, as appropriate.

Supplementary descriptive analyses of disease progression in the 5 years pre-treatment period may be performed to provide additional context to trends observed during the post-treatment period, if retrospective data are available.

Pregnancy analyses

Frequency and outcomes of pregnancies will be tabulated for women in the TEZ/IVA Pregnancy Analyses Cohorts for each year in the post-treatment period.

Drug utilisation analyses

In each calendar year of the study, all patients with a record of TEZ/IVA use in US, Germany, UK , Ireland, and France will be described in terms of age, sex, genotype, $ppFEV_1$, duration of TEZ/IVA exposure (if available), and prior history of CFTR modulator use. Frequency of potential off-label use will be quantified; demographic and clinical characteristics of the potential off-label users will be summarized. If TEZ/IVA labelled indications expand during the course of the study, an additional stratum will be added for the analyses to include the new indicated population (e.g., new on-label users); demographic and clinical characteristics of the new on-label users will be summarized.

Milestones

Five annual analyses reports will be submitted by the end of each December from 2019 through 2023, with each report based on the data through the end of the preceding calendar year (2018 through 2022). Annual reports will include data from the participating registries as available, depending on the status and timeline of product approval and national

	reimbursement decisions.

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

Five annual reports will be submitted by the end of each December from 2019 through 2023, with each report based on analysis of the data through the end of the preceding calendar year (2018 through 2022). Annual reports will include data from the participating registries as available, depending on the status and timeline of product approval and national reimbursement decisions. For instance the first annual study report to be submitted in December of 2019 will include data from the US Cystic Fibrosis Foundation (CFF) registry (based on the marketing authorization and commercial availability of TEZ/IVA in the US in February 2018), however may not include data from participating EU registries depending on timing of approval and reimbursement.

The patient registries make annual data available for analyses between May to June of the following year (after data lock point and data cleaning completion). Analyses, development of tables, figures, and listings and their quality control review are expected to take registries 2 to 3 months to complete. Preparation of an annual study report is expected to take Vertex another 2 months, resulting in report submission by the end of December of each year. Based on the above, the milestones are summarised in Table 1.

Table 1 Study Milestones

Milestone	Planned Date
Start of data collection[a]	June 2019
End of data collection[a]	June 2023
Registration in EU PAS Register	Following Protocol Approval
Year 1 Report (data through December 2018)	End of December 2019
Year 2 Report (data through December 2019)	End of December 2020
Year 3 Report (data through December 2020)	End of December 2021
Year 4 Report (data through December 2021)	End of December 2022
Final report (data through December 2022)	End of December 2023

[a] Per EU Good Pharmacovigilance Practices VIII.B.2, the start and end of data collection for secondary use of data are when the analytical datasets are available.

7 RATIONALE AND BACKGROUND

7.1 Background

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. CF affects over 70,000 individuals worldwide, with approximately 30,000 in the US,[1] 45,000 in the EU,[2] over 4,200 in Canada,[3] and over 3,400 individuals in Australia.[4]

CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which result in absent or deficient function of the CFTR protein at the cell surface.[5] CFTR is an epithelial chloride channel responsible for helping to regulate salt and water absorption and secretion in various tissues (including lung).[6] More than 2000 mutations in the *CFTR* gene have been identified.[7] Mutations have been classified based on the molecular and functional consequence on the CFTR protein[8] and can be generally considered to reduce the quantity of functional protein that reaches the epithelial cell surface or reduce the function of protein located at the cell surface.

Two complementary approaches to increase CFTR-mediated Cl^- secretion in airway epithelia have been studied. One approach is to treat with a compound that will modify the cellular processing and delivery of CFTR protein to the cell surface (CFTR corrector). Another approach is to treat with a compound that increases channel gating activity of protein kinase A-activated CFTR at the cell surface to enhance ion transport (CFTR potentiator). Depending on the amount of residual CFTR channel activity in the membrane and the pathophysiology of that activity (reflecting the CFTR genotype of the patient and possibly other factors), both approaches may be required to ameliorate lung disease in patients with CF.

Tezacaftor (TEZ) and ivacaftor (IVA) combination therapy is a new CFTR corrector / potentiator combination that targets the underlying cause of CF; it is indicated for treatment of CF in patients 12 years and older who have specified *CFTR* mutations and is intended for chronic and potentially lifelong use. In both the EU and the US, the indicated population includes patients who have two copies of the *F508del* mutation. In addition, in the EU, TEZ/IVA is indicated for patients heterozygous for the *F508del* mutation and one of the 14 mutations in which the CFTR protein shows residual activity (referred hereafter as residual function [RF] mutations); in the US, TEZ/IVA is also indicated for patients with at least one copy of one of 26 RF mutations. The list of indicated mutations, by region, is provided in Annex 3.

7.2 Rationale

In Phase 3 studies, a clinically meaningful benefit in patients homozygous for *F508del* and patients heterozygous for *F508del* and an RF mutation was demonstrated across multiple endpoints addressing the key primary goals of CF treatment: improving lung function, reducing pulmonary exacerbations, enhancing nutritional status, and improving quality of life (respiratory symptoms). TEZ/IVA was well tolerated, with no unique safety concerns attributable to TEZ/IVA identified. The favourable benefit-risk profile makes TEZ/IVA an important therapy for the populations covered by the indication.

Phase 3 safety data for approximately 1,000 subjects ≥12 years old who received at least 1 dose of TEZ/IVA, including 326 subjects with at least 48 weeks of exposure, support the favorable safety and tolerability of the regimen. The safety labeling contains no additional warnings and precautions over the currently approved component of the regimen, IVA. TEZ/IVA offers an

improved benefit/risk profile for patients homozygous for *F508del*, including those who cannot tolerate LUM/IVA due to adverse events or drug-drug interactions.

While TEZ/IVA is intended for chronic, potentially lifelong use, safety outcomes and CF disease progression have not been studied beyond the clinical development programme. Furthermore, certain patient sub-populations were excluded from the clinical programme, including pregnant women, patients with advanced liver disease, organ transplant recipients, and patients with severe lung function impairment ($ppFEV_1$ <40 at screening). Understanding of the long term effects in the overall population of patients receiving treatment and in the specified sub-populations will be informative to patients, caregivers, prescribers, and payers. In addition, data are needed to understand the utilisation patterns and describe any potential off-label use of the product in clinical practice.

This 5 year observational post-authorisation safety study (PASS) will evaluate the safety, disease progression, and pregnancy in patients with CF who are treated with TEZ/IVA, as well as its drug utilisation patterns using observational cohorts of patients receiving therapy in a "real-world" setting. Existing CF registries provide an established source to obtain data on long term effects in a real life use for analysis. CF patient registries in the US (the largest worldwide), as well as in Germany and the UK (two of the largest in Europe) include comprehensive clinical data to meet the study objectives.

8 RESEARCH QUESTIONS AND OBJECTIVES

8.1 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, CF complications, pulmonary pathogens, and liver function tests [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 and older, have mutations that are indicated for TEZ/IVA, and are treated with TEZ/IVA
4. To evaluate the drug utilisation and to characterise potential off-label use of TEZ/IVA in patients outside of the labelled indication (e.g., patients who do not have mutations that are indicated for TEZ/IVA)

8.2 Prior Hypotheses

The study will further characterise the effects of long-term TEZ/IVA treatment in real-life use and provide descriptive analyses on specified safety and CF disease progression outcomes using observational data. Because these analyses will be used for general active safety surveillance/hypothesis generation, no prior hypotheses are proposed.

9 RESEARCH METHODS

9.1 Study Design

This is a 5 year observational cohort study using data collected by existing national CF patient registries in the US, Germany, and UK (all study objectives), as well as Ireland and France (drug utilisation objective only) for patients treated with TEZ/IVA.

Within-cohort evaluation of outcomes in the pre-treatment and post-treatment periods will be performed (US, Germany, and UK).

Certain conditions may warrant early study termination prior to the end of the 5 year period. These may include, but are not limited to: 1) decision by regulatory authority; 2) standard of care changes significantly impacting the study design (e.g., significant proportion of patients discontinuing the therapy due to availability of novel CFTR modulators, resulting in a significant decrease of the study population size).

9.1.1 Study Population

The source populations for the study are patients included in the CF registries in the US, Germany, UK, Ireland, and France.

To address the study objectives the following cohorts will be established (Table 2):

1. Longitudinal safety and disease progression analyses cohorts (TEZ/IVA Cohorts; established separately in US, German, and UK registries)
2. Pregnancy Analyses Cohorts (established separately in US, German, and UK registries)
3. Drug Utilisation Cohorts (established separately in US, German, and UK registries, as well as CF registries of Ireland and France)

Table 2 Study cohorts in each registry

Study Cohorts	Country				
	US	**Germany**	**UK**	**Ireland**	**France**
TEZ/IVA Cohorts Safety analyses Disease progression analyses	Yes	Yes	Yes	No	No
Pregnancy Analyses Cohorts (subset of TEZ/IVA Cohorts; female, aged 14years and older)	Yes	Yes	Yes	No	No
Drug Utilisation Cohorts	Yes	Yes	Yes	Yes	Yes

UK: United Kingdom; US: United States

The description of inclusion and exclusion criteria for these cohorts follows.

9.1.2 Inclusion and Exclusion Criteria

Due to its observational nature, this study will have broad inclusion criteria and minimal exclusions. The inclusion criteria are summarized by cohort in Sections 9.1.2.1-9.1.2.3; no additional exclusion criteria will apply to study cohorts.

9.1.2.1 Longitudinal Safety and Disease Progression Analyses Cohorts

These closed cohorts (referred hereafter as TEZ/IVA Cohorts) will include all patients who have a first record of treatment with TEZ/IVA in the registry during the cohort eligibility period, are aged 12 years and older, and have indicated mutations (Annex 3). The cohort eligibility period will be defined as the first calendar year of commercial availability of TEZ/IVA, however if during the first year of commercialisation the uptake of TEZ/IVA is slower/lower than expected, the cohort eligibility period may be extended by one year. Further, if it is determined over the course of study that there are large patient populations of new users that are systematically different from the patients who initiated TEZ/IVA during the cohort eligibility period (e.g. indication expanded to patients ≤12), additional separate cohorts may be established for safety and disease progression analyses.

TEZ/IVA Cohorts will be followed over the course of study duration (2018 through 2022), up to 5 years. For each of the follow-up years, only patients remaining on treatment from the previous year will be included in TEZ/IVA Cohorts.

9.1.2.2 Pregnancy Analyses Cohorts

These cohorts will include all female patients aged 14 years and older from the TEZ/IVA cohorts.

9.1.2.3 Drug Utilisation Cohorts

These cohorts will include all patients in the registries with record of TEZ/IVA use at any time during each of the analysis years. The open cohorts will include all patients from the longitudinal TEZ/IVA cohorts (Section 9.1.2.1) as well as any new users initiating TEZ/IVA during the study period, regardless of patient age or genotype.

9.2 Setting

The US CFF Patient Registry tracks the treatments and health of people with CF across the US. Information is collected on patients who receive care at more than 110 CFF-accredited care centres and agree to participate in the registry. In 2016, the US CFF Patient Registry included over 29,000 CF patients, representing between 81% and 84% of all people with CF in the country.[1, 9]

The German CF Registry is a database of CF patients in Germany maintained by the Mukoviszidose Institute gGmbH (MI). The MI is the operator of the German CF registry and is a non-profit limited company for therapeutic research and development (MI) and is a wholly-owned subsidiary of the Mukoviszidose e.V. (German cystic fibrosis association). The registry aims to record, analyse and improve the CF patients care in Germany. In 2016, the registry included over 5,720 CF patients from 92 CF-sites across Germany, representing approximately over 80% of all CF patients in the country.[10]

The UK CF Registry is an anonymised database of all those with CF in the UK maintained by the UK CF Trust and used to identify patterns and anomalies in CF care and outcomes across the UK. The UK CF Registry database includes data from 30 paediatric and 26 adult CF care centres in England, Scotland, Wales, and Northern Ireland. In 2017, the registry covered more than 99% of UK CF population and included 10,469 patients.[11, 12]

The CF Registry of Ireland (CFRI) represents 94.5% of the known CF population in the Republic of Ireland and included 1,266 patients with CF in 2016.[13]

The French CF Registry (Registre français de la mucoviscidose) represents 88% of the known CF population in France and included approximately 6,757 patients with CF in 2016.[12, 14]

9.3 Variables

All study variables will be derived from the data collected by the registries in pre-specified data collection forms. Data collection forms are approved by the governing committee for each registry and capture pertinent data related to CF and the medical care of patients with CF. Physicians with expertise in CF or other clinical staff from certified CF centres complete the forms according to the data guidelines and indicate the specified diagnoses for patients. Each registry employs its own data entry guideline rather than use external coding dictionaries. Rigorous data cleaning procedures are in place to provide robust data sets for the analyses.

Types of variables important for this analysis include exposure, endpoints, and covariates. The definitions of these variables are not necessarily identical across all participating registries due to the fact that each registry independently determines their data collection elements.

9.3.1 Exposure

TEZ/IVA exposure will be determined by evidence of TEZ/IVA treatment in each participating registry during the study period. Patients will be considered exposed to TEZ/IVA until there is evidence of treatment discontinuation in the registries.

Duration of exposure will be calculated using precise start and stop dates of TEZ/IVA (if available) or based on the dates of the first and last encounters with the evidence of TEZ/IVA use.

Exposure duration will be categorised into meaningful groups, e.g., <6 months, ≥6 to <12 months, and ≥12 months, etc.

9.3.2 Covariates

The covariates listed below will be summarised as a part of descriptive analyses of TEZ/IVA Cohorts and/or will be used as stratification variables for all Objective 1 and 2 analyses:

- Age at index date (date of TEZ/IVA initiation); categorised as appropriate, e.g. ≥12 to <18 years and ≥18 years
- Sex (male versus female)
- Genotype (*F508del/F508del* genotype versus indicated RF genotypes by region as described in Annex 3)
- ppFEV$_1$ during the pre-treatment baseline year (calculated using references published by Global Lung Function Initiative [GLI] standards[15]); defined in US as the average of all available measures for each year, and defined in Germany and UK as best available measurement for each year; categorised as appropriate, e.g. <40, ≥40 to <70, ≥70 to <90, and ≥90)
- Moderate or severe hepatic impairment, defined as cirrhosis with or without portal hypertension (yes versus no)
- Organ transplantation history

- TEZ/IVA exposure duration (categorised as appropriate, e.g. <6 months, ≥6 to <12 months, and ≥12 months, etc.)
- History of CFTR modulator use/exposure, defined as any prior history of IVA or LUM/IVA use (yes versus no)
- CF medications (e.g., chronic antibiotics, dornase alfa, hypertonic saline, bronchodilators, corticosteroids, pancreatic enzymes)

9.3.3 Safety Analyses Endpoints

The following endpoints will be evaluated to address Objective 1 using US, German and UK patient registries:

- **Death** will be defined based on the record in the respective registry. Causes of death will include the following categories: respiratory/cardiorespiratory, liver disease, trauma, suicide, transplant-related, other, and unknown.
- **Organ transplantations** will be defined based on the record in the respective registry. Type of transplant will include the following categories: heart/lung, lung alone, liver, kidney, and other.
- **Hospitalisations** will be defined based on the record in the respective registry. Reasons for hospitalisation will include the following categories, if reported by the registries: pulmonary exacerbation, pulmonary complication other than exacerbation, gastrointestinal (GI) complication, transplant-related, sinus infection, non-transplant surgery, other and unknown.
- **Pulmonary exacerbations (PEx)** will be defined based on the record in the respective registry of intravenous (IV) antibiotic use at home or hospitalisation due to exacerbation.
- **CF complications** will be defined based on the record in the respective registry of any of the CF complications listed in Table 3. Complications will be grouped into the following categories: Cystic fibrosis-related diabetes (CFRD), Hepatobiliary, Pulmonary, Sinus, Bones/Joints, GI, Psychiatric, Renal, Cancer, and Cardiovascular. In addition to grouping complications as shown above, some acute complications will be analysed as stand-alone variables if available from the registries, e.g. acute liver events, and others as warranted.
- **Respiratory microbiology** will include patients with a bacterial culture and evidence of one or more of the organisms listed in Table 4.
- **Liver function tests** will include alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (BILI), and alkaline phosphatase (ALP) as recorded in the registry.

Table 3 CF Complication Categories, by Registry

Complication	US	Germany	UK
CFRD (with or without fasting hyperglycemia, with or without complications)	Yes	Yes	Yes
Hepatobiliary	Yes[1]	Yes[2]	Yes[3]
Acute liver events (acute liver failure or hepatitis)	Yes	**No**	Yes
Hepatic encephalopathy	Yes[4]	**No**	Yes
Pulmonary			

Table 3 CF Complication Categories, by Registry

Complication	US	Germany	UK
Massive (severe) hemoptysis	Yes	Yes	Yes
Pneumothorax	Yes	Yes	Yes
Sinus (sinus disease, nasal polyps, sinus surgery)	Yes	Yes	Yes
Bones/Joints	Yes	Yes	Yes
GI			
DIOS	Yes	Yes	Yes
Pancreatitis	Yes	No	Yes
Psychiatric			
Depression	Yes	Yes	Yes
Anxiety disorder	Yes	Yes	**No**
Renal	Yes	Yes	Yes
Acute kidney injury / renal failure	Yes	**No**	Yes
Cancer	Yes	Yes	Yes
Cardiovascular	**Hypertension only**	**No**	Yes[5]

CF: cystic fibrosis; CFRD: cystic fibrosis related diabetes; DIOS: distal intestinal obstruction syndrome; GI: gastrointestinal; UK: United Kingdom; US: United States

[1] In US registry: liver disease cirrhosis, liver disease non-cirrhosis, acute hepatitis (infectious, non-infectious, unknown), acute liver failure

[2]In German registry: liver disease (non-cirrhosis), liver disease (cirrhosis)

[3]In UK registry: cirrhosis with portal hypertension, cirrhosis with no portal hypertension, liver disease non-cirrhosis, acute hepatitis, acute liver failure, hepatic encephalopathy

[4]In US CF registry, hepatic encephalopathy is captured as cirrhosis complication

[5] In the UK registry: hypertension, arrhythmia, cardiac arrest, cardiomyopathy, congenital heart disease, heart failure, ischemic heart disease, valvular disease

Table 4 Respiratory Microbiology, by Registry

	US	Germany	UK
Pseudomonas aeruginosa	Yes	Yes	Yes
Burkholderia cepacia complex	Yes	Yes	Yes
Stenotrophomonas (Xanthomonas) maltophilia	Yes	Yes	Yes
Staphylococcus aureus	Yes	Yes	Yes
MRSA	Yes	Yes	Yes
Haemophilus influenza (any species)	Yes	Yes	Yes
Aspergillus (any species)	Yes	Yes	Yes
Mycobacterium tuberculosis	Yes	**No**	Yes
Nontuberculous mycobacterium	Yes	Yes	Yes
Klebsiella (any species)	Yes	Yes	Yes
Alcaligenes (Achromobacter) xylosoxidans	Yes	Yes	Yes

Table 4 Respiratory Microbiology, by Registry

	US	Germany	UK

MRSA: methicillin-resistant *Staphylococcus aureus*

9.3.4 Disease Progression Analyses Endpoints

The following endpoints will be evaluated to address Objective 2 using US, German and UK patient registries:

- $ppFEV_1$ (calculated using GLI standards and defined as an average of all available measurements for each analysis year in the US, and the best available measurement for each analysis year in Germany and UK)
- BMI

A number of safety analyses endpoints (e.g. pulmonary exacerbations and hospitalisations) may also be interpreted as measures of disease progression.

9.3.5 Pregnancy Analyses Endpoints

To evaluate the frequency and outcomes of pregnancies in females with indicated genotypes who are treated with TEZ/IVA (Objective 3), pregnancy data will be evaluated as collected in the US, Germany, and UK for female patients aged 14 years and older. Pregnancy outcomes will include live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown. In addition, gestational age and frequency of congenital anomalies (UK only) will be evaluated.

9.3.6 Drug Utilisation Analyses Endpoints

To address Objective 4, TEZ/IVA use outside the labelled indication (e.g., in patients <12 years of age or in patients who do not have indicated *CFTR* mutations [Annex 3]) will be evaluated as a potential off-label use. Off-label use definition will be adjusted for each annual analysis as necessary if labelled indications change.

TEZ/IVA use within any expanded label indications will also be evaluated within these analyses.

9.4 Data Sources

US, German and UK CF registries will be used to address all study objectives. In addition, CF registries in Ireland and France will be used to address the drug utilisation study objective. Section 9.2 provides the high level overview of these patient registries.

9.5 Study Size

Study size will be dependent on the patterns of use of TEZ/IVA in routine clinical practice.

Based on 2017 data, the US CF Foundation registry (largest to be evaluated in this study) had a total of 8,111 patients homozygous for *F508del* aged 12 years or older and 1,512 patients with one of 26 RF mutations indicated in the US aged 12 years and older (of them, a sub-set of 958 patients had one of the 14 RF genotypes indicated in the EU). However, the size of TEZ/IVA treated population can be expected to be smaller reflecting the real-world uptake and availability of alternative CFTR modulators for these patient populations (e.g., LUM/IVA for patients homozygous for *F508del*; IVA in the US for patients with responsive RF mutations).

The size of the population eligible for TEZ/IVA treatment in Germany and the UK is expected to be significantly smaller than in the US CF Foundation registry based on the differences in CF population size as well as indicated genotypes in Europe versus US.

By working with the US, German, and UK patient registries, we expect to be able to analyse over 80% of all eligible patients in the US, Germany, and UK.

9.6 Data Management

Data management is maintained at each registry according to their internal processes. Only final analysis tables (i.e., no patient-level data) will be provided to the marketing authorisation holder.

9.6.1 Data Management for the US CFF Patient Registry

The US CFF imports data from the registry database to the registry server and has processes in place for verifying the data format, modifying data, and removing duplicate records. As a rule, the CFF attempts to do as little corrections to the raw data as possible. Only authorised CFF employees have access to the database. Annual grant awards to CF centres serve as an incentive for the provision of complete, high quality data in the CFF patient registry.

9.6.2 Data Management for the German CF Registry

Patient data are documented in the German CF registry in the online register tool MUKO.web by the participating CF-sites. Data management is done by Interdisciplinary Center for Clinical Trials, University Medical Center Mainz (IZKS). Standardised processes are available to check data quality. Duplicates are regularly merged by the identification management. After the data export, the biometricians of the IZKS carry out data quality checks. Only patients with evidence of at least an annual encounter in the German CF registry database are included in the analyses. Lost-to-follow up checks are carried out.

9.6.3 Data Management for the UK CF Registry

Throughout the year, regular (monthly) data verification and merging of duplicate patient records is carried out by the Registry Team. Following the annual data cut, extensive data cleaning is undertaken in conjunction with the Bio-Statisticians at the CF Trust. Data completeness is assessed annually. For patients known to be alive, 96% have evidence of at least an annual encounter in the UK CF Registry database.

9.6.4 Data Management for the CF Registry of Ireland

CFRI Clinical Research Associates (CRAs) are responsible for the manual collection of required data from each Registry patient's medical chart, at each CF specialist and shared care centre. Data are gathered using a standardised case report form and are entered into the Registry software platform. The CRAs have medical and nursing backgrounds respectively, and are suitably qualified to review and interpret medical information in patient medical charts. The CFRI software was developed using the European CF Patient Registry software, and utilises many of its data management business rules.

9.6.5 Data Management for the French CF Registry

The French CF Registry collects data once a year by means of a questionnaire transmitted using Web, paper questionnaires, or exports from electronic patient files. Since 2008 the French CF Registry has received a qualification by the Registry Evaluation Committee as a valuable database for public health and research. CF centres follow the guidelines for data entry and data

management procedures outlined in the Registry's SOPs. A data validation plan details the list of the checks.

9.7 Data Analyses

This section presents a summary of the planned statistical analyses for this study. Details are presented in a Statistical Analysis Plan (SAP).

To meet the study objectives, data will be analysed separately for each registry over the course of the 5 year study duration (2018 through 2022). The results of the analyses will be presented in the annual study reports. Each annual report will include patient data collected through the end of the previous calendar year.

Descriptive statistics will be presented for all study endpoints. Continuous variables will be summarised using the following descriptive summary statistics, where appropriate: the number of observations (n), mean, standard deviation (SD), standard error (SE), 95% confidence intervals (CI), median, minimum value (min), and maximum value (max). Categorical variables will be summarised using counts, percentages and 95% CI, as appropriate.

All safety and CF disease progression endpoints (Objectives 1 and 2, respectively) will be evaluated in the TEZ/IVA Cohorts in US, German, and UK registries.

9.7.1.1 Definitions of Study Periods

Within TEZ/IVA Cohorts in each registry, pre-treatment and post-treatment periods will be defined as described below and illustrated in Figure 1. The approach will vary depending on whether the registry employs encounter-based data collection which allows for anchoring the periods on the date of TEZ/IVA treatment initiation (US), or uses annual data collection which necessitates analyses based on the calendar years (Germany and UK).

- **Pre-treatment period** will be defined in the encounter-based US registry as the 5 year period before the date of TEZ/IVA treatment initiation (index date). In German and UK registries this period will be defined as 5 calendar years before the cohort eligibility period. Depending on the completeness of retrospective data in the registries, not all patients may have complete 5 years of pre-treatment data on all endpoints; these patients will still be included in the analyses.
  - Within the pre-treatment period, the 12 months immediately preceding TEZ/IVA treatment initiation date (US) or the calendar year immediately preceding the cohort eligibility period (Germany and UK) will be considered as **pre-treatment baseline** year for all analyses of change from baseline.
- **Post-treatment period** in the encounter-based US registry will continue for up to 5 years after TEZ/IVA treatment initiation. In German and UK registries this period will continue for up to 5 calendar years from commercialisation.

Figure 1 Study Periods, US

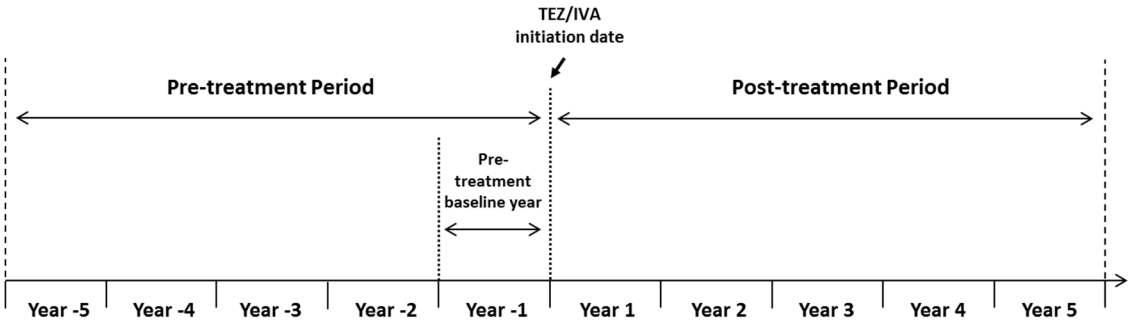
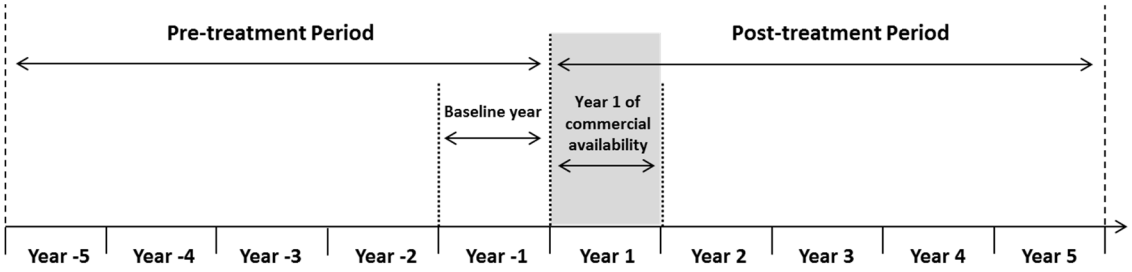


Figure 2 Study Periods, Germany and UK



9.7.1.2 Safety Analyses

All safety analyses outcomes will be evaluated in the TEZ/IVA Cohorts for each registry, and for each year of the post-treatment period, as well as for the pre-treatment baseline year, where appropriate. Analyses will be stratified by patient genotype (*F508del/F508del* genotype versus indicated RF genotypes by region), sex, age at TEZ/IVA treatment initiation (<18 and ≥18 years), baseline ppFEV$_1$ (<40, ≥40 to <70, and ≥70), prior history of CFTR modulator use (IVA use, LUM/IVA use, or no prior CFTR modulator use history), and other variables as appropriate (e.g., moderate to severe hepatic impairment, organ transplant history). Additional in-depth analyses may be performed for outcomes deserving further investigation if sufficient data are available.

Deaths and organ transplants

Proportions of deaths (overall and by cause of death) and corresponding 95% CIs will be calculated for each year of the post-treatment period. For death cases, cause of death and age at death will be summarized descriptively.

Similarly, proportions of organ transplants (overall and by transplant type) and corresponding 95% CIs will be calculated for each year of the post-treatment period.

Hospitalisations and pulmonary exacerbations

Annualized risks (proportions of patients with event) and corresponding 95% CIs will be calculated for hospitalisations (overall and by reason for hospitalisation) and PEx for each year of the post-treatment periods. In addition, annualized rates (average number of events per patient) and corresponding 95% CIs will be calculated.

CF complications

Prevalence and corresponding 95% CIs will be calculated for CF complications by category/type (Table 3) for each year of the post-treatment period.

Pulmonary pathogens

Proportions of patients with bacterial cultures available will be tabulated for each year of the post-treatment period.

Among patients with available bacterial cultures, proportions of patients with positive cultures will be calculated by microorganism (Table 4) for each year of the post-treatment periods.

Liver function tests

Proportions of patients with LFT performed will be tabulated for each year of the post-treatment period to see if patients have different extents of liver function monitoring following TEZ/IVA treatment initiation, potentially resulting in detection bias.

Among patients with LFT performed, proportions of patients with abnormal LFT results (ALT, AST, total BILI, ALP) relative to the upper limit of normal (ULN) will be calculated for each year of the post-treatment period based on the data collected by the registries. In particular, for ALT and AST, proportions of patients with any values during the analysis year exceeding 3, 5 and 8 times the ULN will be tabulated. Similarly, for BILI and ALP, proportions of patients with values exceeding 2 times the ULN will be tabulated.

Supplementary analyses of safety outcomes in the 5 year pre-treatment period

Supplementary descriptive analyses of safety outcomes (except for deaths and transplantations) in the 5 year pre-treatment period may be performed to provide additional context to trends observed during the post-treatment period, if retrospective data are available. The same statistics will be provided for all relevant safety outcomes as described above. Of note, a considerable proportion of patients in all registries are expected to have missing data for some or all of the safety endpoints in most of the years during the 5 year pre-treatment period.

9.7.1.3 Disease Progression Analyses

The evaluation of CF disease progression will be based on assessment of change from pre-treatment baseline over time in lung function ($ppFEV_1$) and BMI in the TEZ/IVA Cohorts, to be summarized in table form and in a visual format appropriate for the data.

Lung function change from pre-treatment baseline

For the baseline year and each year of the post-treatment period, summary statistics (n, mean, SD, SE, 95% CI, median, min and max) for $ppFEV_1$ (average of all available measurements for each analysis year in the US, and best available measurement for each analysis year in Germany and UK) will be tabulated. Changes from the baseline year will also be tabulated. These analyses will be stratified by patient genotype (*F508del/F508del* genotype versus indicated RF genotypes by region), age at TEZ/IVA initiation (<18 and ≥18 years), baseline $ppFEV_1$ (<40, ≥40 to <70, and ≥70), and prior history of CFTR modulator use (IVA use, LUM/IVA use or no prior CFTR modulator use history).

BMI change from pre-treatment baseline

For the baseline year and each year in the post-treatment period, summary statistics (n, mean, SD, SE, 95% CI, median, min and max) for BMI will be tabulated. Changes from the baseline year will also be tabulated. These analyses will be stratified by patient genotype (*F508del/F508del* genotype versus indicated RF genotypes by region), age at TEZ/IVA initiation (<18 and ≥18 years), and prior history of CFTR modulator use (IVA use, LUM/IVA use or no prior CFTR modulator use history).

Supplementary analyses of lung function and BMI patterns in the 5 year pre-treatment period

Supplementary descriptive analyses of disease progression in the 5 years pre-treatment period may be performed to provide additional context to trends observed during the post-treatment period, if retrospective data are available.

Summary statistics (n, mean, SD, SE, median, min and max) for $ppFEV_1$ (average of all available measurements for each analysis year in the US, and the best available measurement for each analysis year in Germany and UK) and BMI will be calculated for each year of the pre-treatment period.

Since these supplementary analyses of the pre-treatment period will be limited to patients with retrospective data available in the registries, in order to understand whether there are systematic differences in the subgroup of patients with complete pre-treatment period data, baseline demographic and clinical characteristics of the overall TEZ/IVA Cohorts will be compared to patients with complete retrospective data available. If warranted, sensitivity analyses restricted to the patient population with non-missing visits and/or assessments in each of the analysis years may be performed.

9.7.1.4 Pregnancy Analyses

Frequency of pregnancies will be tabulated for patients in the TEZ/IVA Pregnancy Analyses Cohorts for each year in the post-treatment period. Among patients with a record of pregnancy, distribution of pregnancy outcomes will be tabulated. In addition, summary statistics for gestational age will be calculated. Frequency of congenital anomalies will be presented for UK only (as these data are not collected by the CF registries in US and Germany).

9.7.1.5 Drug Utilisation Analyses

In each calendar year of the study, patients in Drug Utilisation Cohorts in US, Germany, UK, Ireland and France will be described in terms of age, sex, genotype, $ppFEV_1$, duration of TEZ/IVA exposure (if available), and prior history of CFTR modulator use.

Frequency of potential off-label use will be calculated; demographic and clinical characteristics of potential off-label users will be summarized.

If TEZ/IVA labelled indications expand during the course of the study, an additional stratum will be added for the analyses to include the new indicated population (e.g. new on-label users); demographic and clinical characteristics of new on-label uses will be summarized.

9.8 Quality Control

9.8.1 Quality Control for US CFF Patient Registry

The responsibility for the quality of the US CFF registry data lies with the CF centres. The annual grants application signed by all centre directors has a clause that states that the registry data provided by the centre is accurate to the best of the centre's director knowledge. Some of the

key data entries (e.g., death dates) are verified with the centres' data entry staff after the end of the reporting year. There are also documented evidences about almost-perfect match between the registry data and the data from the clinical studies that involve patients with CF. Since 2013, the CFF conducts an annual audit of 3% to 5% of the registry records for that year as part of their regular processes to ensure registry data quality.

9.8.2 Quality Control for German CF Registry

The responsibility for data quality lies with the CF-sites participating in the registry. This is regulated in a contract between the CF-sites and the registry operator, the MI. In the German CF registry, many of the entries (e.g. size, weight, FEV_1) are automatically checked for correctness by plausibility checks. The plausibility checks are further expanded in the coming years. All changes to entries in the registry are recorded in an audit trail. Data cleaning and data management is done by IZKS. IZKS sends data queries to the CF-sites. Since 2018 on-site monitoring visits are established and around 5% of the data documented in the registry are considered in this quality assurance process.

9.8.3 Quality Control for UK CF Registry

The UK patient registry has regular quality testing by the hosting company with respect to the encryption and safety of the data held. The application is held in the EU in accordance with EU recommendations. There are elaborate encryption protocols in the production of user access including a unique person-specific username and unique password. The password has to be changed every 30 days. The data can only be viewed by the user site, and data cannot be moved between sites without involvement of the Registry Team.

The registry is operated in a password-protected, locked office in accordance with the ethical requirements. The Registry Team are "*trusted third parties*" and conform to the Data Protection Act in full. Centres and clinics are monitored on a regular basis by the Registry Team. Study monitoring visits are scheduled with the sites on a regular basis to ensure that data are recorded in the patient notes as well as on the registry, in accordance with usual practice. All entries are checked to ensure accuracy. Any discrepancies are documented and verified with the sites. Random sets of patients' notes are also checked to ensure no bias in the registry data. Registry Team conduct regular monthly data verification. A Registry Helpdesk is available to respond within 24 hours to queries; all sites are encouraged to use this Helpdesk. The Registry Team is available by e-mail and phone.

9.8.4 Quality Control for the CF Registry of Ireland

The CFRI use trusted third parties authorised to gather clinical information from the Health Service Executive and the Central Statistics Office. CFRI has inbuilt error-checking functionality to reduce potential errors at the point of data entry e.g., limit checks for height and weight. The CRA's cross-check data entry values against data for the previous hospital encounter, and major differences are checked. FEV_1 value and percent predicted collected from medical charts are automatically checked according to an agreed algorithm, and genotype data are cross-checked against hard copies of genetic lab reports on file at the CFRI. Further data quality control checks are performed at annual intervals. Annual datasets are cleaned prior to data analysis for Annual Report preparation. Standard operating procedures/protocols and automated quality control checks provided by the European CF Society Patient Registry are also utilised for submission of Irish data to the European CF Registry.

9.8.5 Quality Control for the French CF Registry

The French CF Registry performs data quality checks when the data are collected with paper questionnaires or on xml files, while the data are being entered on the online secured questionnaire and after entry into the registry database (with the SAS software). Checks include, for example, missing or incoherent dates, missing important clinical data, implausible numeric values. Queries are sent to the centres and corrections are implemented on the online entry software as necessary.

Death data are checked individually against the national database on death certificates. Diagnostic data are compared with the database of the French NBS program. Mutations are checked with the database of the national genetic laboratories. The Registry database also hosts specific questionnaires on pregnancies and on the *Burkolderia Cepacia* complex, allowing for comparing data between those questionnaires and the annual questionnaire.

9.9 Limitations of the Research Methods

Limitations of within-group study design

This study relies on within-cohort evaluation of outcomes in the pre- and post-treatment periods. In the absence of a concurrent comparator group, interpreting the post-treatment changes in select outcomes in this population of patients with progressive disease may be challenging and may need additional context.

To provide such further context to the observed disease progression patterns following treatment initiation, supplementary descriptive analyses of the disease progression in the 5 year pre-treatment period may be performed. These analyses will be limited by the fact that not all patients who initiate TEZ/IVA treatment will have 5 years of complete data before treatment initiation captured in the registries. The baseline demographic and clinical characteristics of the overall TEZ/IVA Cohort and the sub group of patients with the complete 5 years of pre-treatment data may be compared to understand if there are any systematic differences, and any potential biases discussed accordingly.

As such, this study should be considered hypotheses-generating rather than hypothesis-testing.

Limitations of missing data

Due to the observational nature of this study, some patients may have missing visits and/or assessments (e.g., $ppFEV_1$ measurements). Data may be missing from either the pre-treatment or post-treatment periods. All registries included in this study have robust systems in place to minimise missing data. To further address this limitation, sensitivity analyses restricting the patient population to those with non-missing data in both periods may be performed. No imputations of missing data will be conducted in the course of statistical analyses.

Other limitations of registry data

As this study relies solely on the existing, routinely collected registry data, several potential safety concerns cannot be evaluated. For instance, cataracts or concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers cannot be assessed due to lack of data collection or insufficient level of detail being collected in the registries. These potential safety concerns will be monitored via the pharmacovigilance activities as described in the TEZ/IVA Risk Management Plan (RMP).

Information regarding clinical trials participation is not sufficiently captured in the registries (e.g., no information is captured on specific trials subjects participate in). As a result, the number of potential off-label users may be over-estimated in the drug utilisation analyses performed as a part of this study. This is because “off-label” users may indeed include patients who are enrolled in TEZ/IVA clinical studies but are not identifiable as such in the registries.

Furthermore, registries do not provide the precision of a clinical study where all patients have clinical visits and assessments (e.g. pulmonary function testing) at a defined and frequent interval; the precise dates of TEZ/IVA exposure start and complications development among the patients contributing data to the registries may not be available; data collected may not always allow for the differentiation between the incident and prevalent (pre-existing) complications.

9.10 Other Aspects

The study duration is expected to be 5 years. Certain conditions may warrant early study termination. These may include, but are not limited to: 1) decision by regulatory authority; 2) standard of care changes significantly impacting the study design (e.g., significant proportion of patients discontinuing the therapy due to availability of novel CFTR modulators, resulting in a significant decrease of the study population size).

10 PROTECTION OF HUMAN SUBJECTS

Patient registries are managed in accordance with the ethical principles founded in the Declaration of Helsinki and in accordance with local applicable laws and regulations.

In addition to complying with the Declaration of Helsinki, the US CFF maintains confidentiality and strictly enforce all regulations specified by the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

In addition to complying with the Declaration of Helsinki, the German Cystic fibrosis association maintains confidentiality and strictly enforce all national regulations.

To safeguard the well-being and rights of the patients, the UK CFT will comply with all relevant laws of the European Union that are directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the CF Registry is located. These include, but are not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical trials, the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects" (1996 version), and the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

10.1 Subject Information and Informed Consent

Subject information is obtained and maintained by the patient registries. Vertex will not have access to subject information. Informed consent/assent is obtained as part of each registry enrolment procedures. Procedures in this study are determined to be covered by the existing patient consent for participation in US, Germany, UK, Ireland and France registries.

Subjects and their parent or legal guardian are informed that participation is voluntary and that they may withdraw from the registry at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent and assent (as applicable) are recorded in the subject's medical record or a study/clinic chart. Once all of their questions have been answered and they have voluntarily agreed to participate in the registry, each patient or patient's parent or legal guardian (as applicable) is asked to sign and date the informed consent form (ICF) and assent (as applicable). Informed consent and assent (as applicable) must be obtained from each patient or the patient's parent or legal guardian (as applicable) before the performance of any registry-related activity. A copy of the completed ICF and assent (as applicable) is provided to the subject or the parent or legal guardian.

In the US, institutional review board (IRB) reviews all appropriate documentation to safeguard the rights, safety, and well-being of the subjects.

In Germany, each patient signs an informed consent form in full compliance with applicable law and which permits the disclosure of the analysed data, authorises and allows the use of the data.

In the UK, the CF Registry consent procedures have been agreed upon with the National Research Ethics Service.

In Ireland, after ethics committee approval, informed consent is signed by (or on behalf of) the patient before data are collected by CFRI. The information in CFRI is held confidentially, with a CFRI-exclusive (private), encrypted server hosted in a secure building.

In France, each patient signs an informed consent form in full compliance with applicable law and which permits the disclosure of the analysed data, authorises and allows the use of the data.

10.2 Access to Records

Vertex will not have access to patient records.

10.3 Subject Privacy

To maintain subject confidentiality, all analyses will be presented to Vertex using de-identified data.

Although data are received at the US CFF with patient identifiers (e.g., name, last 4 digits of social security number) to ensure that the database is comprehensive and free of duplicate records, identifiable information is not released. Information from the registry will be shared with other researchers only if researchers receive approval of their research proposals by both the CF Registry Committee and the researcher's IRB. However, name, social security number, or other direct identifiers will not be released.

All information in the German cystic fibrosis registry is collected in accordance with the national legal requirements (DSVGO: Datenschutzgrundverordnung) and treated confidentially. The registry procedure has been positively reviewed by the responsible data protection authorities. The registry is maintained in accordance with applicable laws and ethical guidelines. In the German Cystic Fibrosis Registry, identifying data of the patients are recorded and a unique pseudonym is generated from these data. This ensures that only one data record per patient will be analysed even if a patient is treated in several outpatient CF-sites.

All the information in the UK CF Registry is held confidentially. The CF Registry is registered under the Data Protection Act (1998) and has Research Ethics Committee approval. It is

managed in accordance with relevant laws and ethical guidelines. The Registry needs to hold information that can identify the patient (name, date of birth, and postcode) so that the patient's own hospital can enter the information and use it to monitor the patient's care and to ensure that patient information is not recorded more than once. This information is used to generate an anonymous number so that patients cannot be identified when the information from each clinic is brought together to give the overall picture of CF in the UK.

The CFRI conforms to the Data Protection Act (1988) and holds information that can identify the patient (name, date of birth, and address) so that the patient may request his/her own records. Global patient reports summarising total numbers of patients are anonymised. Users of these data must be approved by the Executive Council of the CFRI after review of the submitted protocol.

In France, the registry includes semi-anonymous patient identification. Statistical analysis is performed on anonymised data.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional study based on the secondary use of data and thus reporting of suspected adverse reactions as individual case safety reports (ICSRs) is not required as per Guideline on Good Pharmacovigilance Practices, Module VI – Management and reporting of adverse reactions to medicinal products. Any reports of adverse events / reactions will only be summarised in the study reports, where applicable.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Synopses of annual and final study reports will be annexed to Annex 9 of the RMP. Study results will be used to adjust the safety specification (Part II-SV) and the pharmacovigilance plan (Part III) of the RMP as appropriate. In addition, interim and final study results will be periodically and critically discussed in Periodic Safety Update Report and also summarised in the Development Safety Update Report.

Vertex plans to publish the study results after the final study analysis is completed in collaboration with the registry partners no later than 18 months after the close of the current study (which shall be defined as the final lockdown of all data and the resolution of all queries). Final study results will also be posted at EU PAS register no later than 12 months after the study close.

13 REFERENCES

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14 ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference	Date	Title
1.	Statistical Analysis Plan	2018	Statistical Analysis Plan for IA1, IA2, IA3, IA4, and IA5
2.	CF Foundation – Data Collection Form	2016	2016 CF Foundation Patient Registry Data Collection Forms
3.	German CF Registry Data Collection Form	2016	2016 German CF Registry Data Collection Forms
4.	CF Trust – Data Collection Form	2016	2016 CF Trust Patient Registry Data Collection Forms

15 ANNEX 2. EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE CHECKLIST FOR STUDY PROTOCOLS

16 ANNEX 3. LIST OF *CFTR* GENOTYPES INDICATED FOR TEZ/IVA BY REGION

Indicated genotypes, US	Indicated genotypes, EU
F508del/F508del	*F508del/F508del*
At least one copy of one of the following mutations: *P67L* *R117C* *L206W* *R352Q* *A455E* *D579G* *711+3A→G* *S945L* *S977F* *R1070W* *D1152H* *2789+5G→A* *3272-26A→G* *3849+10kbC→T* *E56K* *R74W* *D110E* *D110H* *E193K* *R347H* *E831X* *F1052V* *K1060T* *A1067T* *F1074L* *D1270N*	One copy of *F508del* and one copy of the following mutations: *P67L* *R117C* *L206W* *R352Q* *A455E* *D579G* *711+3A→G* *S945L* *S977F* *R1070W* *D1152H* *2789+5G→A* *3272-26A→G* *3849+10kbC→T*