Post-Authorisation Safety Study Information

VERTEX PHARMACEUTICALS INCORPORATED

Title	An Observational Study to Evaluate the Utilisation Patterns and Long-term Effects of Lumacaftor and Ivacaftor Combination Therapy in Patients With Cystic Fibrosis
Version identifier	Version 1.2
Date	29 April 2016
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	Lumacaftor (VX-809) and ivacaftor (VX-770)
Medicinal Product	Orkambi™; lumacaftor/ivacaftor (200 mg/125 mg fixed-dose combination [FDC]) tablets
Product Reference	EMEA/H/C/003954
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 are 12 years and older, homozygous for the *F508del-CFTR* mutation and treated with Orkambi (i.e., death, organ transplant, hospitalisations, pulmonary exacerbations, CF complications [including but not limited to hepatobiliary, cardiac arrhythmia, hypertension], and liver function tests [LFTs]). 2. To evaluate the frequency and outcome of pregnancies in female patients who are 14 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi. 3. To evaluate CF disease progression in patients who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi as measured by changes over time in percent predicted forced expiratory volume in 1 second (FEV_1) and other clinical signs of disease progression (e.g., body mass index [BMI], CF related diabetes [CFRD], distal intestinal obstruction syndrome [DIOS], hospitalisation, and pulmonary exacerbations). 4. To evaluate the drug utilisation and to characterise potential off-label use of Orkambi in patients outside of the labeled indication (e.g., patients younger than 12 years of age or patients who are not homozygous for the *F508del-CFTR* mutation). Secondary Objectives (for Primary Objective 1): 1. To evaluate safety outcomes in the following subgroups of patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi: a. Patients with FEV_1 <40% predicted b. Patients with cardiac disease c. Patients with moderate or severe hepatic impairment

	d. Patients with a history of organ transplant 2. To evaluate respiratory microbiology in patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation and treated with Orkambi
Country(-ies) of Study	United Kingdom (UK), United States (US), Ireland, and France
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABPA	allergic bronchial pulmonary aspergillosis
BMI	body mass index
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFRD	cystic fibrosis-related diabetes
CFT	Cystic Fibrosis Trust
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
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
FEV_1	forced expiratory volume in 1 second
GERD	gastroesophageal reflux disease
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
ICF	informed consent form
IRB	institutional review board
LFT	liver function test
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SAP	Statistical analysis plan
TFL	tables, figures, and listings
UK	United Kingdom
US(A)	United States (of America)

3 RESPONSIBLE PARTIES

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Registry Investigator(s)	Dr. Diana Bilton, Cystic Fibrosis Trust (CFT), United Kingdom (UK) Dr. Bruce Marshall, Cystic Fibrosis Foundation (CFF), United Sates (US) Dr. Edward McKone, CF Patient Registry, Ireland Dr. Virginie Colomb-Jung, CF Patient Registry, France

4 ABSTRACT

Title	An Observational Study to Evaluate the Utilisation Patterns and Long-term Effects of Lumacaftor 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. At present, there is no cure for CF. CF affects approximately 70,000 individuals worldwide and is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*), which result in absent or deficient function of the CF transmembrane conductance regulator (CFTR) protein at the cell surface. The lumacaftor/ivacaftor combination therapy (Orkambi) is indicated for treatment of CF in patients 12 years and older who are homozygous for *F508del* mutation in the *CFTR* gene. While Orkambi is intended for chronic, potentially lifelong use, the Phase 3 clinical programme involved 1,108 patients with CF exposed to the combination therapy for up to 120 weeks. Furthermore, certain patient sub-populations were excluded from the clinical programme, including pregnant women, patients with a history of certain cardiac disease, patients with advanced liver disease, organ transplant recipients, and patients with severe lung function impairment (forced expiratory volume in 1 second [FEV_1] < 40% predicted at screening). Understanding long-term effects in the overall population of patients receiving treatment and in the specified sub-populations will be informative to patients and their parents, prescribers, and payers. Existing CF registries provide an established source to obtain data on long-term effects in a real-world use for analysis.
Research Questions and Objectives	Primary Objectives: 1. To evaluate safety outcomes in patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi (i.e., death, organ transplant, hospitalisations, pulmonary exacerbations, CF complications [including but not limited to hepatobiliary, cardiac arrhythmia, hypertension], and liver function tests [LFTs]). 2. To evaluate the frequency and outcome of pregnancies in female patients who are 14 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi. 3. To evaluate CF disease progression in patients who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi as measured by changes over time in percent predicted forced expiratory volume in 1 second (FEV_1) and other clinical signs of disease progression (e.g., body mass index [BMI], cystic-fibrosis related diabetes [CFRD], distal intestinal obstruction syndrome [DIOS], hospitalisation, and pulmonary exacerbations). 4. To evaluate the drug utilisation and to characterise potential off-label use of Orkambi in patients outside of the labeled indication (e.g., patients younger than 12 years of age or patients who are not homozygous for the *F508del-CFTR* mutation).

	Secondary Objectives (for Primary Objective 1): 1. To evaluate safety outcomes in the following subgroups of patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi: a. Patients with FEV_1 <40% predicted b. Patients with cardiac disease c. Patients with moderate or severe hepatic impairment d. Patients with a history of organ transplant 2. To evaluate respiratory microbiology in patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation and treated with Orkambi
Study Design	Five-year observational cohort study using data collected by existing national CF patient registries in the UK and US (all study objectives), as well as Ireland and France (drug utilisation objective only).
Study Population	Patients included in the existing US and UK CF patient registries are the source population for all study analyses. To address the study objectives, the following cohorts will be established in these registries: **1. Safety analyses cohorts:** 1.1. Orkambi Safety Cohort will include all patients aged 12 years and older who are homozygous for the *F508del-CFTR* mutation and have received treatment with Orkambi during the analysis year. 1.2. Comparator Safety Cohort will include all patients aged 12 years and older who are heterozygous for the *F508del-CFTR* mutation with a Class I/II mutation on the second allele and who have never received Orkambi or Kalydeco™. **2. Pregnancy analyses cohorts:** 2.1. Orkambi Pregnancy Analyses Cohort will include all female patients aged 14 years and older from the Orkambi Safety Cohort. 2.2. Comparator Pregnancy Analyses Cohort will include all female patients aged 14 years and older from the Comparator Safety Cohort. **3. Disease progression analyses cohorts:** 3.1. Orkambi Disease Progression Cohort will include all patients from the Orkambi Safety Cohort with the exclusion of those with lung transplantation history. Each subsequent analysis year cohort will include only those patients who were members of the previous year Orkambi Disease Progression Cohort. 3.2. Comparator Disease Progression Cohort will include all patients from the Comparator Safety Cohort with the exclusion of those with lung transplant history. Each subsequent analysis year cohort will include only those patients who were members of the previous year Comparator Disease Progression Cohort. **4. Drug utilisation cohorts:** All patients in the registries with record of Orkambi use at any time during the analysis year. Of note, in addition to UK and US registries, drug utilisation cohorts will be established in the CF registries of Ireland and France.

Variables	**Exposure**
	Orkambi exposure as recorded in the registries
	
	Endpoints
	<u>Safety analyses endpoints:</u>
	• Death, organ transplant, hospitalisations, pulmonary exacerbations
	• CF complications, including, but not limited to
	  o Hepatobiliary
	  o Pulmonary
	  o Cardiac, including cardiac arrhythmias (UK only)
	  o Hypertension
	  o Bones / Joints
	  o CF-related diabetes (CFRD)
	  o Gastrointestinal
	• Respiratory microbiology
	• Liver function tests (LFTs)
	
	<u>Pregnancy analyses endpoints:</u>
	• Pregnancy outcome
	• Gestational age, congenital anomalies (if available)
	
	<u>Disease progression analyses endpoints:</u>
	• Percent predicted FEV_1, clinical signs of CF disease progression (e.g., CFRD, DIOS, BMI)
	
	<u>Drug utilisation analyses endpoints:</u>
	• Orkambi use outside of labelled indications
	
	Covariates
	• Age, gender
	• Percent predicted FEV_1; defined in US and UK as best available measurement for the analysis year
	• Moderate or severe hepatic impairment
	• Cardiac disease (UK only)
	• Organ transplantation history
	• Orkambi exposure duration

Data Sources	Data sources will include: 1. UK CF Registry (all study objectives) 2. US CFF Patient Registry (all study objectives) 3. CF Registry of Ireland (drug utilisation objective) 4. CF Registry of France (drug utilisation objective)
Study Size	Study size will depend on the patterns of use of Orkambi in routine clinical practice. Based on 2013 data, the UK CF registry has approximately 3,003 patients homozygous for *F508del-CFTR* mutation and the US CF Foundation registry had 8,526 patients homozygous for *F508del-CFTR* mutation aged 12 years and older.
Data Analysis	To meet the study objectives, data will be analysed separately for each registry for 5 years. The results of the annual analyses will be combined by Vertex in a single study report for each year. Each annual report will include the patient data collected during the previous calendar year. Descriptive statistics will be presented for all study endpoints.

	All safety, pregnancy, and CF disease progression endpoints (Objectives 1, 2, and 3, respectively) will be compared between the respective Orkambi and Comparator Cohorts. Risks, as well as crude relative risks with 95% confidence intervals will be calculated for safety outcomes for each of the analyses years. Analyses will be stratified by patient age, percent predicted FEV_1, and other variables as appropriate. Multivariate modelling and sensitivity analysis may be performed for outcomes deserving further investigation if sufficient data are available.
Milestones	Annual analyses reports will be submitted each December from 2017 through 2021.

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

The patient registries make annual data available for analyses at between May to June of the following year (after data lock point and data cleaning completion). Analyses, development of tables, figures, and listings (TFLs) 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 in 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 2017 (date when US CFF Registry 2016 data will become available for analyses)
End of data collection[a]	June 2020
Registration in EU PAS Register	Upon Final Protocol Approval
Year 1 Report (2016 outcomes data)[b]	December 2017
Year 2 Report (2017 outcomes data)	December 2018
Year 3 Report (2018 outcomes data)	December 2019
Year 4 Report (2019 outcomes data)	December 2020
Final report of study results (2020 outcomes data)	December 2021

[a] Per EU Good Pharmacovigilance Practices VIII.B.2, the start of data collection in case of secondary use of data is the date from which data extraction starts and end of data collection is when the analytical datasets are completely available.

[b] Orkambi was launched in US in July 2015. Evaluating 2015 outcomes data among patients who initiated therapy in the second half of the year and thus exposed for less than 6 months on average is not considered meaningful. To allow for the product uptake and sufficient exposure duration, the first annual report will focus on evaluating 2016 outcomes data among patients exposed to Orkambi (regardless of the time of initiation). Depending on reimbursement status, Year 1 report will also include data from the UK, Ireland, and France.

7 RATIONALE AND BACKGROUND

7.1 Introduction

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,[1] with approximately 30,000 in the US[1], 36,000 in the EU[2], over 4,000 in Canada[3], and over 3,200 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] At present, there is no cure for CF, and despite adjunctive treatments with nutritional supplements, antibiotics, and mucolytics,[7] the median predicted age of survival for a person born today with CF is approximately 37 to 41 years of age.[8, 9]

More than 2000 mutations in the *CFTR* gene have been identified.[10] Mutations in the *CFTR* gene have been classified based on the molecular and functional consequence on the CFTR protein[11, 12] 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.

The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR). In the US, 86.4% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation and about 46.5% have 2 copies.[9] In the EU, approximately 82.7% of patients with CF have 1 or 2 copies of the *F508del-CFTR* mutation, and approximately 51.3% of patients with CF in the UK have 2 copies.[8, 13] The *F508del-CFTR* mutation interferes with the ability of the CFTR protein to reach and remain at the cell surface, as well as to open and close, resulting in decreased chloride ion (Cl^-) transport.[14, 15] The combined effect is a marked reduction in F508del-CFTR-mediated Cl^- secretion that impairs fluid regulation and promotes accumulation of thick, sticky mucus in the airway. The mucus build-up obstructs the airways and predisposes the patient to chronic lung infections.[16]

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.

Lumacaftor is a compound developed by Vertex that has been shown to have CFTR corrector properties. Ivacaftor is a compound developed by Vertex that has been shown to have CFTR potentiator properties. The combination of lumacaftor and ivacaftor has recently been shown to be effective in 2 large, Phase 3, randomised studies of subjects with CF who are homozygous for the *F508del* mutation (VX12-809-103, VX12-809-104).[17] The combination therapy (Orkambi) is indicated for treatment of CF in patients aged 12 years and older who are homozygous for *F508del* mutation in the *CFTR* gene.

7.2 Rationale

Safety results from VX12-809-103 and VX12-809-104 studies reported on a pooled basis for each dosing arm across the studies showed that the combination regimens were generally well tolerated.[17] The most common adverse events (AEs), regardless of treatment group, were infective pulmonary exacerbations of CF, cough, headache and increased sputum, and AEs that occurred more frequently in patients who received the combination regimens than those who received placebo were generally respiratory in nature and included dyspnoea and respiration abnormal. Across the 2 studies, elevated liver enzymes (greater than 3 times the upper limit of normal) were observed in 5.2% of subjects who received combination therapy compared to 5.1% of those who received placebo.[17] Seven subjects who received combination therapy had serious AEs related to abnormal liver function tests (LFTs), compared to zero subjects who received placebo. Following discontinuation or interruption of the combination treatment, LFTs returned to baseline for 6 of the 7 subjects and the 7th subject's LFTs improved substantially.[17]

Efficacy results from the development programme showed that combination therapy has a broad array of benefits for subjects aged 12 and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Phase 3 studies showed that for subjects who received the combination regimens compared to placebo, there were statistically significant reductions in the rates of pulmonary exacerbations and improvements in BMI.

While Orkambi is intended for chronic, potentially lifelong use, the Phase 3 clinical programme involved 1,108 patients with CF exposed to the combination therapy for up to 120 weeks. 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 a history of certain cardiac disease, patients with advanced liver disease, organ transplant recipients, and patients with severe lung function impairment (FEV_1 <40% predicted 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 and their parents, 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 Orkambi, 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. US and UK patient registries are two of the largest worldwide and include comprehensive 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 are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi (i.e., death, organ transplant, hospitalisations, pulmonary exacerbations, CF complications

[including but not limited to hepatobiliary, cardiac arrhythmia, hypertension], and LFTs).

2. To evaluate the frequency and outcome of pregnancies in female patients who are 14 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi.
3. To evaluate CF disease progression in patients who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi as measured by changes over time in percent predicted FEV_1 and other clinical signs of disease progression (e.g., BMI, CFRD, DIOS), hospitalisation, and pulmonary exacerbations.
4. To evaluate the drug utilisation and to characterise potential off-label use of Orkambi in patients outside of the labeled indication (e.g., patients younger than 12 years of age or patients who are not homozygous for the *F508del-CFTR* mutation).

Of note, although current study populations for Objectives 1 to 3 include patients who are 12 years and older and homozygous for the *F508del-CFTR* mutation, the population maybe adjusted and expanded if the Orkambi indication extends to cover other patient groups. Study populations for each annual analysis will be described in detail in each Statistical Analysis Plan (SAP).

8.2 Secondary Objectives (for Primary Objective 1)

1. To evaluate safety outcomes in the following sub-groups of patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation, and treated with Orkambi:
   a. Patients with FEV_1 <40% predicted
   b. Patients with cardiac disease
   c. Patients with moderate or severe hepatic impairment
   d. Patients with a history of organ transplant
2. To evaluate respiratory microbiology in patients with CF who are 12 years and older, homozygous for the *F508del-CFTR* mutation and treated with Orkambi

8.3 Prior Hypotheses

The study will further characterise the effects of long-term Orkambi 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 retrospective cohort study using data collected by existing CF patient registries in US and UK (all objectives), as well as Ireland and France (drug utilisation objective).

Existing CF registries in US and UK were considered as an optimal data source to obtain safety, pregnancy and disease progression outcome information in a real-world setting for analysis. They are 2 of the largest national CF registries worldwide encompassing a majority of the patients in the indicated population. Data collected are extensive, and reasonably consistent with one another. The data collected for each year are available for analyses the following year. This approach has successfully been used for the Kalydeco PASS.

9.1.1 Study Population

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

To address the study objectives the following cohorts will be established:

1. Safety analyses cohorts (US and UK registries):
   1.1. Orkambi Safety Cohort
   1.2. Comparator Safety Cohort
2. Pregnancy analyses cohorts (US and UK registries):
   2.1. Orkambi Pregnancy Analyses Cohort
   2.2. Comparator Pregnancy Analyses Cohort
3. Disease progression analyses cohorts (US and UK registries):
   3.1. Orkambi Disease Progression Cohort
   3.2. Comparator Disease Progression Cohort
4. Drug utilisation cohorts (US, UK, Ireland, and France registries)

9.1.2 Inclusion and Exclusion Criteria

9.1.2.1 Safety Cohorts

	Orkambi Safety Cohorts (US and UK registries)	**Comparator Safety Cohorts (US and UK registries)**
Inclusion	• Homozygous for the *F508del* mutation • Patients aged 12 years and older • Treated with Orkambi during analysis year	• Heterozygous for the *F508del* mutation (Class I/II mutation for the second allele) • Patients aged 12 years and older • Never treated with Orkambi or Kalydeco
Exclusion	Participation in Vertex interventional study during analysis year (if such data available)	• Homozygous for the *F508del* mutation • Participation in Vertex interventional study during analysis year (if such data available)

9.1.2.2 Pregnancy Cohorts

	Orkambi Pregnancy Cohorts (US and UK registries)	Comparator Pregnancy Cohorts (US and UK registries)
Inclusion	• Patients in Orkambi Safety Cohort • Female gender • 14 years of age and older	• Patients in Comparator Safety Cohort • Female gender • 14 years of age and older
Exclusion	None	None

9.1.2.3 Disease Progression Cohorts

	Orkambi Disease Progression Cohorts (US and UK registries)	Comparator Disease Progression Cohorts (US and UK registries)
Inclusion	• Patients in Orkambi Safety Cohorts • Each subsequent analysis year cohort includes only those patients who were members of the previous year cohort	• Patients in Comparator Safety Cohorts • Each subsequent analysis year cohort includes only those patients who were members of the previous year cohort
Exclusion	History of lung transplantation	History of lung transplantation

9.1.2.4 Drug Utilisation Cohorts

	Drug Utilisation Cohorts (US, UK, Ireland and France registries)
Inclusion	All patients in the registries with record of Orkambi use at any time during the analysis year
Exclusion	None

9.2 Setting

The US and UK CF patient registries are the largest in the geographic regions covered by the current study.

The UK CF Registry is an anonymised database of all those with CF in the UK. This database is maintained by the UK CFT. It is an invaluable tool that is used by the CFT to identify patterns and anomalies in CF care and outcomes across the UK.[8] The UK CF Registry database includes data from more than 32 paediatric and 28 adult CF care centres in England, Scotland, Wales, and Northern Ireland. The registry covers 100% of UK CF patients and represents a total of about 10,000 of 36,000 patients with CF in the EU.[8]

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.[9] The US CFF Patient Registry includes approximately 28,000 CF patients, representing about 90% of all people with CF in the country.[9]

In both UK and US registries, investigators are physicians at certified CF care centres and all patients participate in standard data collection for assessments for death, organ transplantation, hospitalisations, complications, pulmonary exacerbations, respiratory microbiology, pregnancy, and pulmonary function. Both registries use an online registry application for data entry by staff at CF-accredited care centres. Data collection forms

capture pertinent data related to CF and the medical care of patients with CF. Changes to data collection forms have been incorporated over the years using a process where changes requested by investigators are reviewed and approved by the governing committee for each registry.

The CF Registry of Ireland (CFRI) represents 92.5% of the known CF population in the Republic of Ireland and includes 1,158 patients with CF (approximately 3% of the CF population in the EU), of which 654 are homozygous for the *F508del* mutation.[18]

The French CF Registry (Registre français de la mucoviscidose) represents >90% of the known CF population in France and include approximately 6,046 patients with CF (approximately 18% of the CF population in the EU), of which approximately 2,593 are homozygous for the *F508del* mutation.[13, 19]

9.3 Variables

All study variables will be derived from the data collected by the registries in pre-specified data collection forms. Investigators (physicians with expertise in CF) 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.

The UK CF Trust and US CFF independently determine the data to be collected within UK and US patient registries respectively; thus, the specific variables included in the analyses for this study are not necessarily identical. Types of variables important for this analysis include exposure, endpoints, and covariates.

9.3.1 Exposure

Orkambi exposure will be determined by evidence of Orkambi treatment at any time during the analysis year and patients will remain exposed until there is evidence of treatment discontinuation in the patient registry.

When start and stop dates are available, as in the UK CF Registry, exposure duration will be calculated in days. When start and stop dates are not available, algorithms will be used to extrapolate duration of exposure based on timing of patient encounters and drug exposure data available. The exposure algorithm includes the following rules: if only month and year are available, then the assumed start or stop date will be the 15th of the month or if only year is available, then the assumed start or stop date will be June 30th.

Because start and stop dates are not available from the US CFF Patient Registry, the algorithm to extrapolate duration of exposure includes the following rules: the date of the first encounter with evidence of Orkambi exposure will be used as the start date. Patients will be identified as exposed to Orkambi until a medications form is completed where Orkambi treatment is not reported. The Orkambi stop date will be the first encounter date where exposure is not indicated.

In the analyses, Orkambi exposure will be categorised into the meaningful groups based on the distribution of exposure, such as <6 months, ≥6 to <12 months, and ≥12 months, etc.

9.3.2 Covariates

The covariates below will be summarised as a part of descriptive analyses of study cohorts and will also be used as stratification variables for all Objective 1 analyses:

- Age (defined as age as of 01 January for each analysis year; categorised as ≥12 to <18 years and ≥18 years)
- Gender (male versus female)
- Percent predicted FEV_1 (calculated using references published by Global Lung Function Initiative (GLI) standards[20]); defined in US and UK as best available measurement for the analysis year; categorised as <40%, ≥40% to <70%, and ≥70%)
- Moderate or severe hepatic impairment (defined in UK as cirrhosis with or without portal hypertension, and in US as 'liver disease, cirrhosis')
- Cardiac disease (in UK only, as reported in CF complications form)
- Organ transplantation history
- Orkambi exposure duration (will be summarized for Orkambi Safety Cohorts only, categorised as <6 months, 6 to 12 months, and ≥12 months, etc.)

Additional covariates summarized as part of descriptive analyses of study safety cohorts will include record of the following medication use: chronic antibiotics, dornase alfa, hypertonic saline, bronchodilators, and corticosteroids.

Additional covariates for disease progression analyses will include

- Medications use in the baseline year (chronic antibiotics, dornase alfa, hypertonic saline, bronchodilators, and corticosteroids), and
- Baseline percent predicted FEV_1 (calculated using GLI standards; defined as the best available measurement for the baseline year; categorised as <40%, ≥40% to <70%, and ≥70%).

9.3.3 Safety Analyses Endpoints

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

- **Death** will be defined if there is evidence of a date of death in the registry. Cause of death will include respiratory/cardiorespiratory, liver disease, trauma, suicide, transplant-related, other, and unknown.

  Note: In the UK CF patient registry, death from transplant-related Bronchiolitis Obliterans will be included in the "Other" category.

- **Organ transplantations** will be defined if there is evidence of organ transplantation in the registry. Type of transplant will include lung, liver, and other.

- **Hospitalisations** will be defined if there is evidence of a start date for a hospitalisation.
  - For patients in the US CFF patient registry, reasons for hospitalisation will be evaluated as recorded in the registry database (reasons include pulmonary exacerbation, pulmonary complication, gastrointestinal (GI) complication, transplant-related, sinus infection, non-transplant surgery, and other).
  - Similarly, for patients in the UK CF patient registry, reasons for hospitalisation will be evaluated
- **Pulmonary exacerbations** will be defined by evidence of a CF care episode with reason pulmonary exacerbation.
- **CF complications** will be defined by evidence of any of the CF complications listed in Table 2. Complications will be grouped into the following categories: Cardiac (in UK, and only if the data are sufficient in US), CFRD, Hepatobiliary, Bones/Joints, Pulmonary, GI, and Other as shown in Table 2. In addition to grouping complications as shown above, events of interest may be analyzed as stand-alone variables, e.g. events like cardiac arrhythmia (UK only), hypertension, acute hepatic 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 3.
- **Liver function tests** will include alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (BILI), and alkaline phosphatase (ALP) as recorded in the registry.

Table 2 CF Complications, by Registry

Complication	UK CF Registry Variables	US CF Foundation Registry Variables
Cardiac disease	• Arrhythmia • Cardiac arrest • Cardiomyopathy • Congenital heart disease • Heart failure • Ischemic heart disease • Valvular disease • Other	Not collected systematically as a variable

CFRD status	• CFRD with or without fasting hyperglycemia
	• CFRD complications:
	  ○ Retinopathy
	  ○ Microalbuminuria
	  ○ Other
	• Impaired glucose tolerance
		• CFRD with or without fasting hyperglycemia
		• CFRD secondary complications:
		  ○ Retinopathy
		  ○ Microalbuminuria
		  ○ Chronic renal insufficiency
		  ○ Chronic renal failure requiring dialysis
		  ○ Peripheral neuropathy
		• Impaired glucose tolerance

Table 2 CF Complications, by Registry

Complication	UK CF Registry Variables	US CF Foundation Registry Variables
Hepatobiliary	• Cirrhosis with portal hypertension • Cirrhosis with no portal hypertension • Gallbladder disease • GI bleeding from varices • Liver disease, non-cirrhosis • Acute hepatitis • Acute liver failure • Hepatic encephalopathy	• Gall stones • Gall stones, requiring surgery/procedure • Liver disease, cirrhosis • Complications related to cirrhosis: o Esophageal varices o Gastric varices o GI bleed related to varices o Splenomegaly o Hypersplenism o Ascites o Encephalopathy • Liver disease, non-cirrhosis • Acute hepatitis o Infectious o Non-infectious o Unknown • Acute Liver Failure • Hepatic steatosis • Liver disease, other
Bones/Joints	• Arthritis • Arthropathy • Bone fracture • Cough fracture • Osteopenia • Osteoporosis	• Arthritis/arthropathy • Bone fracture • Osteopenia • Osteoporosis
Pulmonary	• ABPA • Asthma • Hemoptysis, massive • Pneumothorax requiring chest drain • Pulmonary abscess	• ABPA • Asthma • Hemoptysis, massive • Pneumothorax, requiring chest tube
GI	• DIOS • Fibrosing colonopathy/colonic structure • GERD • GI non-varices as source • Pancreatitis • Peptic ulcer • Rectal prolapse	• DIOS • Fibrosing colonopathy/colonic structure • GERD • GI bleed requiring hospitalisation, non variceal • Pancreatitis • Peptic ulcer disease • Rectal prolapse
Other	• Depression • Cancer • Hearing loss • Hypertension • Kidney stones • Nasal polyps • Acute kidney injury requiring dialysis • Chronic kidney disease	• Anxiety disorder • Depression • Cancer confirmed by histology • Hearing loss • Hypertension • Kidney stones • Nasal polyps requiring surgery • Renal failure requiring dialysis

Table 2 CF Complications, by Registry

Complication	UK CF Registry Variables	US CF Foundation Registry Variables
	• Sinus disease • Septicaemia • Other	• Sinus disease (symptomatic) • Other

ABPA: allergic bronchial pulmonary aspergillosis; CFRD: cystic fibrosis related diabetes; DIOS: distal ileal obstruction syndrome; GERD: gastroesophageal reflux disease; GI: gastrointestinal

Table 3 Respiratory Microbiology, by Registry

	UK CF Registry Variables	US CF Foundation Registry Variables
Pseudomonas aeruginosa	• Mucoid • Non-mucoid • Unknown	• Mucoid • Non-mucoid • Mucoid status unknown
Burkholderia cepacia complex	• *B cenocepacia* • *B multivorans* • Other *Burkholderia cepacia*	• *B cenocepacia* • *B multivorans* • *Burkholderia – other (B cepacia, B dolosal, B pyrrocinia, B latens, B seminalis, B pseudomallei, B stabilis, B anthina, B ubonensis, B lata, B contaminans, B vietnamiensis, B ambifaria, B arboris, B metallica, B diffusa)*
Stenotrophomonas (Xanthomonas) maltophilia	• *Stenotrophomonas (Xanthomonas) maltophilia*	• *Stenotrophomonas (Xanthomonas) maltophilia*
Other Pseudomonas species	• Other *Pseudomonas* species	• Other types: o *Pseudomonas mendocina* o *Pseudomonas putida* o *Pseudomonas stutzeri* o *Pseudomonas pseudoalicaligenes* o *Pseudomonas species* – other
Staphylococcus aureus	• *Staphylococcus aureus*	• *Staphylococcus aureus*
MRSA	• MRSA	• *Staphylococcus aureus* o MRSA
Haemophilus influenza (any species)	• *Haemophilus influenza* (any species)	• *Haemophilus influenza* (any species)
Aspergillus (any species)	• *Aspergillus (any species)*	• *Aspergillus (any species)*
Mycobacterium tuberculosis	None mapped	• Mycobacterial species o *Mycobacterium tuberculosis*
Nontuberculous mycobacterium	• Nontuberculous mycobacterium	• Mycobacterial species o *Mycobacterium abscessus/chelonae* o *Mycobacterium avium complex* o *Mycobacterium fortuitum group* o *Mycobacterium gordonae* o *Mycobacterium kansasii*

Table 3 Respiratory Microbiology, by Registry

	UK CF Registry Variables	US CF Foundation Registry Variables
		○ *Mycobacterium marinum* ○ *Mycobacterium terrae*
Escherichia coli	• *Escherichia coli*	None mapped
Klebsiella (any species)	• *Klebsiella (any species)*	• Other types ○ *Klebsiella pneumonia* ○ *Klebsiella species* – other
Other Gram negative	• Other Gram negative	• Other types ○ *B gladioli* ○ *Acinetobacter baumannii* ○ *Acinetobacter species other* ○ *Agrobacterium species* ○ *Bordetella species* ○ *Brevundimonas species* ○ *Chryseobacterium species* ○ *Cupriavidus metallidurans* ○ *Cupriavidus pauculus* ○ *Cupriavidus respiraculi* ○ *Delftia acidovorans* ○ *Delftia species other* ○ *Enterobacter species* ○ *Inquilinus limosus* ○ *Ochrobactrum species* ○ *Ralstonia insidiosa* ○ *Ralstonia pickettii* ○ *Ralstonia species other* ○ *Serratia marcescens*
Alcaligenes (Achromobacter) xylosoxidans	• *Alcaligenes (Achromobacter) xylosoxidans*	• *Alcaligenes (Achromobacter) xylosoxidans*
Pandoria	• *Pandoria*	• Other types ○ *Pandoraea apista* ○ *Pandoraea norimbergensis* ○ *Pandoraeapulmonicola* ○ *Pandoraea sputorum* ○ *Pandoraea* species other
Other	• Other	• *Exophiala dermatitidis* • *Herbaspirillum frisingense* • *Herbaspirillum seropedicae* • *Streptococcus milleri* • *Candida* • *Scedosporium species*

CF: cystic fibrosis; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*

9.3.4 Pregnancy Analyses Endpoints

Pregnancy will be defined if there is evidence of pregnancy in the registries during the analysis year. Pregnancy data are collected in US and UK for female patients aged 14 years and older. Outcomes include live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown. In addition, gestational age (US and UK) and frequency of congenital anomalies (UK only) will be evaluated.

As US CFF Patient Registry does not collect information on congenital abnormalities, registry pregnancy analyses will be supplemented by the summary of the pregnancy reports in Vertex Safety database. As part of routine pharmacovigilance activities, Vertex collects unsolicited reports of pregnancy using the Pregnancy Safety Information Collection Form (see Stand-alone Document 1 in Annex 1).

9.3.5 Disease Progression Analyses Endpoints

Disease progression endpoints will include the following:

- CFRD status (present or absent, as recorded in both registries; in addition, impaired glucose tolerance and secondary CFRD complications may be summarized)
- DIOS (present or absent, as recorded in both registries; no indicators of the DIOS severity are collected by the registries)
- percent predicted FEV_1 (calculated using GLI standards and defined as best available measurement for the analysis year)
- BMI

Other measures of disease progression (e.g., pulmonary exacerbations and hospitalisations) will be evaluated as warranted.

9.3.6 Drug Utilisation Analyses Endpoints

Off-label use will be defined as Orkambi use outside of labeled indication (e.g., in patients less than 12 years of age or in patients who are not homozygous for *F508del-CFTR* mutation).

9.4 Data Sources

UK and US CF registries will be used to address all study objectives. UK CF Registry database includes data from more than 97 paediatric and 35 adult CF care centres in England, Scotland, Wales, and Northern Ireland. The registry covers 100% of UK CF patients. The US CFF Patient Registry includes data from more than 110 CFF-accredited care centres in the US. Data are collected for all patients who consent to participate (about 90% of all US CF patients). Both registries utilize the online registry application, for data entry by staff at CF-accredited care centres.

In addition, CF registries in Ireland and France will be used to address the drug utilization study objective. The French CF Registry (Registre français de la mucoviscidose) represents >90% of the known CF population in France. The CFRI represents 92.5% of the known CF population in the Republic of Ireland.

9.5 Study Size

Study size will be dependent on the patterns of use of Orkambi in routine clinical practice. Based on 2013 data, the US CFF Patient Registry included 8,526 patients 12 years and older who were homozygous for *F508del-CFTR* mutation (target population) and 3,193 patients older than 12 years of age who were heterozygous for *F508del-CFTR* mutation with Class I/II mutation on the second allele (comparator population). The UK CF Registry has around 3,003 and 756 patients in the target and comparator populations, respectively.

Such a sample size in each registry would be sufficient to provide at least an 80% power to detect relative risk of 2 or higher for events with an annual frequency of 2% in the comparator group (for most events of interest for the analysis), assuming most of eligible patients are on Orkambi therapy.

By working with UK and US patient registries, we expect to be able to analyse over 90% of all eligible patients in the US and about a third of all eligible patients in the EU, collectively representing over 60% of all the patients worldwide.

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 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 Imperial College London. Data completeness is assessed annually. For patients known to be alive, 89% have evidence of at least an annual encounter in the UK CF Registry database.

9.6.2 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.

9.6.3 Data Management for the CF Registry of Ireland

CFRI Clinical Research Associates (CRA) are responsible for the manual collection of required data from each Registry patient's medical chart, at each CF specialist and shared care centre. Staff uses a standardised case report form to gather data, and thereafter enter data 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.

9.6.4 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

To meet the study objectives, data will be analysed separately for each registry for 5 years (annual analyses from 2017 through 2021 based on the 2016-2020 data, respectively). The results of the annual analyses will be combined by Vertex in the study reports. Each annual report will include patient data collected by the registries during the previous calendar year.

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

Safety, pregnancy, and CF disease progression endpoints (Objectives 1, 2, and 3, respectively) will be compared between the respective Orkambi and Comparator Cohorts.

Potential confounders and effect modifiers will be evaluated in stratified analysis and multivariate analysis may be carried out as appropriate. Potential confounders and effect modifiers to be evaluated will include but will not be limited to patient demographics (age, gender), baseline lung function, organ transplantation history, presence of hepatic impairment, and cardiac disease (UK only). Other variables may also be evaluated as potential confounders / effect modifiers for specific outcomes deserving further investigation as appropriate (e.g., concomitant medications, prior history of relevant comorbidity, etc.).

This section presents a summary of the planned statistical analyses for this study. Details are presented in a SAP.

9.7.1.1 Safety Analyses (Objective 1)

Each year, risks of death, organ transplantations, hospitalisations, CF complications and pulmonary exacerbations will be calculated for Orkambi Safety Cohort and Comparator Safety Cohort and will be compared by estimating crude relative risks with 95% confidence intervals.

Analyses will be stratified by patient age, gender, percent predicted FEV_1 (best available measurement for the analysis year), cardiac disease (UK only), hepatic impairment, and history of organ transplantation. For Orkambi Safety Cohort, additional stratification by duration of Orkambi exposure will be done for all the safety outcomes.

Risk of death will be presented by cause of death; risk of transplantation by type of transplant; and hospitalisations will be presented by reason for hospitalisation (in US only as UK only collects hospitalisations due to pulmonary exacerbations).

Frequencies of respiratory microorganisms will be calculated for Orkambi and Comparator Safety Cohorts.

Frequencies of LFTs performed and LFTs elevations (ALT, AST, BILI, ALP) relative to the upper limit of normal will be calculated for Orkambi and Comparator Safety Cohorts 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 upper limit of normal will be tabulated for each cohort. Similarly, for BILI and ALP, proportions of patients with values exceeding 2 times the upper limit of normal will be tabulated. Proportions of patients with LFT performed will be estimated for both cohorts and patients with and without LFT performed will be compared within each cohort to see if Orkambi and Comparator patients have different extent of liver function monitoring, potentially resulting in detection bias.

Multivariate modelling may be performed for safety outcomes deserving further investigation if sufficient data are available. In addition, sensitivity analyses may be performed as warranted excluding patients taking part in clinical trials over the course of the study.

9.7.1.2 Pregnancy Analyses (Objective 2)

Frequency and outcomes of pregnancies will be analysed for women in the Orkambi and Comparator Pregnancy Study Cohorts. Pregnancy outcomes include live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown. In addition, gestational age (US and UK) and frequency of congenital abnormality (UK only) will be presented.

9.7.1.3 Disease Progression Analyses (Objective 3)

The evaluation of CF disease progression will be based on examining the temporal trends in lung function, BMI, CFRD, and DIOS in the Orkambi Disease Progression Cohorts and the Comparator Disease Progression Cohorts in US and UK. Other measures of disease progression (e.g. pulmonary exacerbations and hospitalisations) may be evaluated as warranted.

For the purposes of disease progression analyses, measure prior to the start of Orkambi treatment will be considered “baseline”. Each year summary statistics (n, mean, SD, median, minimum and maximum) for best available measure of percent predicted FEV_1, as well as for changes from “baseline” will be tabulated. Analyses will be stratified by patient age (<18 and ≥18 years) and “baseline” FEV_1 (<70% and ≥70%).

Severity of lung function impairment will be tabulated using 3 different categories for each analysis year and for “baseline”: mild/ normal (FEV_1 ≥70%), moderate (FEV_1 is ≥40% to <70%), severe (FEV_1 <40%).

Proportion of patients with CFRD and DIOS, as well as hospitalisations and pulmonary exacerbations will be tabulated for each analysis year and for the baseline year.

Summary statistics (n, mean, SD, median, minimum and maximum) for BMI will be tabulated for each analysis year and for “baseline”. Analyses will be stratified by age (<18 and ≥18 years).

9.7.1.4 Drug Utilisation Analyses (Objective 4)

Each year, patients in Drug Utilisation Cohorts in UK, US, Ireland and France will be described in terms of age, sex, genotype, percent predicted FEV_1 and duration of Orkambi exposure.

Orkambi off-label use will be defined as use in patients outside of the labeled indication (e.g., among patients less than 12 years of age or in patients with mutations other than homozygous *F508del-CFTR*). Off-label use definition will be adjusted for each annual analysis as necessary if labelled indications change. Frequency of off-label use will be calculated and demographic characteristics of off-label users will be described. Safety outcomes among potential off-label users in US and UK may be summarised if patient counts permit.

9.8 Quality Control

9.8.1 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.

9.8.2 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.

9.8.3 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.

9.8.4 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 cepacia complex, allowing for comparing data between those questionnaires and the annual questionnaire.

9.9 Limitations of the Research Methods

Limitations of observational study design

The nature of observational studies with non-random treatment assignment allows for the concern of confounding factors. Whilst patients indicated to be treated with Orkambi are of different genotype from comparator patients, feasibility assessment showed that they are similar in terms of demographic characteristics, lung function, and annual risk of death. Nevertheless, residual confounding by unknown / unmeasured factors is possible, especially if there is a differential uptake of Orkambi in the indicated population. If warranted, patients in Orkambi cohorts may be further matched to Comparator patients on demographic and disease severity characteristics. As such, study should be considered hypotheses-generating rather than hypothesis-testing.

Another limitation of the study design is possible differential follow-up of the Orkambi and Comparator Cohorts in routine practice, which could introduce ascertainment bias of outcomes. It cannot be excluded that patients initiating novel therapies like Orkambi are followed more closely than untreated patients and as a result more adverse outcomes get detected.

Additionally, because eligibility for a cohort is determined each year, a patient may be included in different cohorts over the course of this study. This would limit the ability to

include this patient in longitudinal evaluations, such as for change in lung function over time.

Limitations of missing data

Missing data may introduce misclassification of exposure and outcomes in observational studies. The UK and US patient registries have robust systems in place to minimise missing data. For UK registry, 89% of patients known to be alive have evidence of at least an annual encounter in the database. Amongst those, 95% have evidence of pulmonary function measure. For the US registry, 85% to 95% of patients' records in 2013 had verification for different medications data, 91% had complications data, and 93.1% had microbiology data. Additionally, 96% of CF non-transplant patients 6 years or older and known to be alive had recorded pulmonary function test data.

Experience from the Kalydeco Long-term Safety Study shows that the potential missing data issue is minimal for the important endpoints of interest, for instance, less than 3.5% of subjects treated with ivacaftor in 2014 had missing pulmonary function measurements in both registries.

No imputations of missing data will be conducted in the course of statistical analyses, however, if deemed necessary and applicable, sensitivity analyses based on endpoints of interest may be performed to evaluate the potential s that missing data may have had on the results.

Other data limitations

Other limitations of the data collected by the registries include the following:

- Information regarding clinical trials participation is not sufficiently captured in the registries (e.g., no information is captured on specific trial subjects participate in). As a result, in the drug utilisation analyses performed as a part of this study the number of potential off-label users may be over-estimated. This is because “off-label” users may indeed include patients younger than 12 years of age or with other *CFTR* genotypes (other than homozygous *F508del*) who are enrolled in Orkambi clinical studies but are not identifiable as such in the registries.
- The precise dates of exposure start and complications development among the patients contributing data to the registries may not be available. In the encounter-based US registry, date of patient encounter when exposure to therapy or complication is first recorded is used as a proxy. In the UK Registry, exposure start and stop dates are recorded, but similarly to US, precise dates may not be available for select complications. The potential impact of this imprecision on the study analyses is limited to the first calendar year of patients’ exposure to the product, when a possibility cannot be excluded that some events occurring during that year precede the exposure initiation. In the following years, as this is a chronic long-term therapy, this potential issue is minimal to none. As was the case with the Kalydeco PASS first annual analyses, further sensitivity analyses may be performed to understand the magnitude and potential impact of any pre-treatment event inclusions.
- While LFT abnormalities data collected by the registries have been limited historically, MAH’s discussions with the UK CF Registry and US CFF Patient

Registry resulted in agreement to update the data collection forms (implemented as of 2016) to collect more detailed data on liver chemistries (ALT, AST, ALP, GGT, BILI).

- Registries do not provide the precision of a clinical study where all patients have pulmonary function testing at a defined and frequent interval; instead, best available percent predicted FEV_1 for each analysis year will be used.
- Registries do not predefine the clinical presentations that constitute a pulmonary exacerbation. Therefore, there is likely some variability in pulmonary exacerbation events within each registry and across both registries.
- The analyses must rely on outcomes as collected/defined by the registries, which do not always allow differentiation between incident and prevalent endpoints.

9.10 Other Aspects

The study duration is expected to be 5 years. Certain conditions may warrant 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., comparator patients initiating novel therapies).

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.

To safeguard the well-being and rights of participants in this PASS, 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).

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).

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 enrollment procedures. Procedures in this study are determined to be covered by the existing patient consent for participation in US, 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 UK, the CF Registry consent procedures have been agreed upon with the National Research Ethics Service.

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

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.

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.

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.

The CFRI conform with 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 (GVP), 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 Risk Management Plan (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 UK CF Trust and US CFF 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 report will also be posted at EU PAS register no later than 12 months after the study close.

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14 ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference	Date	Title
1.	Vertex Form WI-0519c (Version 2.0)	2015	Pregnancy Safety Information Collection Form

15 ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS