1 POST-AUTHORISATION SAFETY STUDY INFORMATION

VERTEX PHARMACEUTICALS INCORPORATED

Title	An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients With Cystic Fibrosis
Version identifier	2.2
Date	08 May 2013
EU PAS Register Number	Study will be registered in EU Post-authorisation Study (PAS) Register following PRAC approval of final protocol, and before study initiation.
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Medicinal Product	Kalydeco
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Procedure Number	N/A
Marketing Authorisation Holder(s)	Vertex Pharmaceuticals (UK) Ltd.
Joint PASS	No
Research Question and Objectives	1. To evaluate the long-term safety of ivacaftor in patients with cystic fibrosis (CF) 2. To evaluate frequency and outcomes of pregnancy in ivacaftor-treated patients 3. To evaluate the drug utilisation of ivacaftor 4. To evaluate CF disease progression in ivacaftor-treated patients
Country(-ies) of Study	United Kingdom (UK), United States (US)
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABPA	allergic bronchial pulmonary aspergillosis
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
DIOS	distal intestinal obstruction syndrome
ECFS	European Cystic Fibrosis Foundation
ECFSPR	European Cystic Fibrosis Foundation Patient Registry
EMEA	European Medicines Agency
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
$FEF_{25\%-75\%}$	forced midexpiratory flow
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
G551D	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
G551D	CFTR protein with a replacement of a glycine residue at position 551 with an aspartic acid residue
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GVP	Good Pharmacovigilance Practices
ICF	informed consent form
IRB	institutional review board
NTM	nontuberculous mycobacteria
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
tbd	to be determined
UK	United Kingdom
US(A)	United States (of America)
USPI	United States Prescribing Information

3 RESPONSIBLE PARTIES

Principal Investigator	Dr. Diana Bilton, Cystic Fibrosis Trust, United Kingdom (UK)
	Dr. Bruce Marshall, Cystic Fibrosis Foundation, United Sates (US)
Coordinating Investigator(s)	Elaine Gunn, Clinical Care and Cystic Fibrosis Registry Manager, Cystic Fibrosis Trust, UK
	Christopher Dowd, Cystic Fibrosis Foundation, US

Note: The principal investigators and the coordinating investigators will be responsible for data collection, data analyses, and reviewing yearly reports. The marketing authorisation holder will be responsible for producing and submitting the yearly reports.

4 ABSTRACT

Title An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients With Cystic Fibrosis

Clinical 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, and at present, there is no cure. Cystic fibrosis 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.

Ivacaftor (Kalydeco™; 150-mg tablets) was approved in the United States and the European Union (EU) in 2012 for the treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene. Ivacaftor is an orally bioavailable small molecule CFTR potentiator that targets the underlying defect in CF. As such, ivacaftor is a member of a new class of drugs - CFTR modulators - that provide a new therapeutic approach to the treatment of CF. Ivacaftor is the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF.

Ivacaftor is intended for chronic, potentially lifelong use. Understanding of the long-term effects will be informative to patients and their parents, prescribers, and payers. Existing CF registries provide an established source to obtain long-term safety in a real-life use for analysis. The patient registries of the CF Trust in the United Kingdom (UK) and the CF Foundation in the United States (US) provide the ideal source to obtain long-term safety information because the data collected are extensive and consistent with one another. In addition, the patients with CF from the CF Trust and the CF Foundation patient registries encompass a majority of the patients in the indicated population.

Other EU patient registries were considered for this study, and a separate feasibility assessment and subprotocol are provided.

Research Questions and Objectives

Primary Objectives

1. To evaluate the long-term safety of ivacaftor in patients with CF
2. To evaluate outcomes of pregnancy in ivacaftor-treated patients
3. To evaluate the drug utilisation of ivacaftor
4. To evaluate CF disease progression in ivacaftor-treated patients

Secondary Objectives for Primary Objective 1

1. To evaluate the long-term safety of ivacaftor amongst patients in the following subgroups:
   - Patients between 6 and 11 years of age
   - Patients with forced expiratory volume in 1 second (FEV_1) <40% predicted value
   - Patients with cardiac disease
   - Patients with moderate or severe hepatic impairment
2. To evaluate pulmonary exacerbations and bacterial sputum colonisation in patients with long-term ivacaftor treatment

Secondary Objective for Primary Objective 2

To measure the frequency of pregnancy in ivacaftor-treated patients

Secondary Objectives for Primary Objective 3

Off-label use amongst patients within the following subgroups:

- Children less than 6 years of age
- Patients with Class III, non-*G551D-CFTR* mutations
- Patients with non-Class III mutations

Secondary Objectives for Primary Objective 4

To evaluate the effect of ivacaftor on CF disease progression, as measured by

- CF lung disease severity, based on pulmonary function (e.g., percent predicted FEV_1)
- Clinical signs of CF disease progression (e.g., death, transplantation, CF-related diabetes [CFRD], distal intestinal obstruction syndrome [DIOS])
- Change in lung function over time

Prior Hypotheses

This study provides descriptive analyses on specific safety outcomes using observational data from patient registries. These analyses will be used for hypothesis generation if safety issues are observed and warrant future study. Therefore, no prior hypotheses are proposed for the primary objectives. Prior hypothesis is provided for specific secondary objectives, although the study may be underpowered to detect any differences:

- Pulmonary exacerbations: similar or lower incidence in the Ivacaftor Cohort than the Comparator Cohort and previously observed in the pivotal Phase 3 studies (as described in the SmPC)
- Adverse drug reactions (as listed in the SmPC): similar or lower incidence in the Ivacaftor Cohort than the Comparator Cohort and previously observed in

the pivotal Phase 3 studies (as described in the SmPC)

- Serious adverse events and adverse events leading to withdrawal of ivacaftor: similar or lower incidence in the Ivacaftor Cohort than the Comparator Cohort (CF Trust data only).

Study Design

Patient registries established by the CF Trust and the CF Foundation will be used for this study. Whilst patient data collected at patient registries are encounter-based, the data will be used as a secondary data source for this study, with an annual analysis conducted by the patient registry staff on data collected in the previous year. These registries are disease registries of observational cohort design.

Six (6) cohorts will be included in the study:

1. The Ivacaftor Cohort will include all ivacaftor-treated patients enrolled in the CF Trust or CF Foundation patient registries, regardless of age, *CFTR* genotype, or pulmonary function.
2. The Comparator Cohort will include patients who are not receiving and have never received ivacaftor and are a match on age group, *CFTR* genotype class, and sex to patients in the Ivacaftor Cohort.
3. The Historical Cohort will include patients who have the *G551D-CFTR* mutation, were enrolled in the patient registries in 2008 (before ivacaftor was available in clinical studies and commercially in the UK and the US), and have no evidence of exposure to ivacaftor.
4. The Ivacaftor Pregnancy Study Cohort will include all female patients 13 years of age or older who were enrolled in the patient registries and were treated with ivacaftor.
5. The Comparator Pregnancy Study Cohort will include female patients who have never been exposed to ivacaftor and are a match on *CFTR* genotype class to patients in the Ivacaftor Pregnancy Cohort.
6. The Drug Utilisation Cohort will include all patients who were enrolled in the patient registries with evidence of ivacaftor exposure.

Study Population

Specific inclusion and exclusion criteria for the 6 cohorts in this study are provided as follows.

Ivacaftor Cohort

- Inclusion Criteria
  1. Patients with CF in the CF Trust or the CF Foundation patient registries
  2. Patients treated with ivacaftor
- Exclusion Criterion
  1. Participation in an interventional study during the analysis period (if available)

Comparator Cohort

- Inclusion Criteria
  1. Patients with CF in the CF Trust or the CF Foundation patient registries
  2. Patients with no evidence of ivacaftor exposure (current or past)
  3. Patients matched to patients in the Ivacaftor Cohort on age group, *CFTR* genotype class, and sex
- Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

Historical Cohort

- Inclusion Criteria
  1. Patients with CF in the CF Trust or the CF Foundation patient registries
  2. Patients with *G551D-CFTR* mutation
  3. Patients with no evidence of ivacaftor exposure before ivacaftor was available commercially
- Exclusion Criterion
  1. Participation in an interventional study during the analysis period (if available)

Ivacaftor Pregnancy Study Cohort

- Inclusion Criteria
  1. Female patients with CF in the CF Trust or the CF Foundation patient registries
  2. Patients 13 years of age or older
  3. Patients treated with ivacaftor
- Exclusion Criterion
  1. Participation in an interventional study during the analysis period (if available)

Comparator Pregnancy Study Cohort

- Inclusion Criteria
  1. Female patients with CF in the CF Trust or the CF Foundation patient registries
  2. Patients 13 years of age or older
  3. Patients with no evidence of ivacaftor exposure (current or past)
  4. Patients matched on *CFTR* genotype class to patients in the Ivacaftor Pregnancy Study Cohort
- Exclusion Criterion
  1. Participation in an interventional study during the analysis period (if available)

Drug Utilisation Cohort

- Inclusion Criteria
  1. Patients with CF in the CF Trust or the CF Foundation patient registries
  2. Patients with current evidence of ivacaftor exposure
- Exclusion Criterion
  1. Participation in an interventional study during the analysis period (if available)

Variables In both registries, all patients participate in standard encounter-based data collection including annual assessments for exposure, death, organ transplantation, hospitalisations, CF complications, pulmonary exacerbations and respiratory microbiology, pregnancy, and pulmonary function. (However, the CF Trust Patient Registry only includes annual data for each patient.) Investigators at CF care centres enter data for their enrolled patients with CF into the registry databases. To meet the study objectives, data for safety- and disease

progression-related outcomes will be analysed separately for each registry for 5 years.

Exposure

Ivacaftor exposure, as reported by CF physician to the patient registry

Endpoints

1. Safety:
   - Death
   - Organ transplant
   - Hospitalisations
   - CF complications including but not limited to hepatobiliary, gastrointestinal, and pulmonary conditions
   - Pulmonary exacerbations and respiratory microbiology
   - Serious safety outcomes
2. Pregnancy
   - Live birth
   - Stillbirth
   - Spontaneous abortion
   - Therapeutic abortion
   - Gestational age
   - Congenital anomalies
3. Drug utilisation
   - Ivacaftor exposure in patients with CF
4. CF disease progression
   - CF lung disease severity based on percent predicted FEV_1
   - Clinical signs of CF disease progression
   - Change in lung function over time

Data Sources

1. CF Trust Patient Registry (UK)
2. CF Foundation Patient Registry (US)

In both registries, all patients participate in standard encounter-based data collection including annual assessments for death, organ transplantation, hospitalisations, complications, pulmonary exacerbations, respiratory microbiology, pregnancy, and pulmonary function. Investigators at CF care centres enter data for their enrolled patients with CF into the registry databases. In both registries, investigators are physicians at certified CF care centres. Data collection forms were developed to 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 data elements collected are provided in standard terms for diagnoses and treatments and are considered adjudicated diagnoses.

Additional data sources (European CF Society Patient Registry and national registries in Ireland, France, and Germany) were evaluated (see Annex 3). Based on the completed feasibility assessment, these data sources are appropriate for the drug utilisation analysis (Objective 3).

Study Size

Ivacaftor is indicated for the treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene. The estimated prevalence of the *G551D* mutation is approximately 2374 patients globally. Based on 2010 data, the CF Trust has enrolled 432 patients with the *G551D* mutation[1] and the CF Foundation has enrolled 1035 patients with the *G551D* mutation.[2] A Comparator Cohort will be identified for each registry's Ivacaftor Cohort at a ratio of m:1, where m is the maximum number of matches available. The Historical Cohort will comprise patients with the *G551D* mutation who do not have evidence of treatment with ivacaftor through clinical studies.

Data Analysis

To meet the study objectives, data for safety-related outcomes will be analysed separately for each registry for 5 years (data "extraction" in 2013 to 2017 of patient data collected at sites in 2012 to 2016, respectively). All enrolled patients exposed to ivacaftor (Ivacaftor Cohort) and matched comparators (Comparator Cohort) will be included in the study analyses at each yearly report. As a reference, a Historical Cohort (patient data from 2008) will be included in the study analyses at the first yearly report.

Data analyses will be performed by the CF Trust and CF Foundation to support the study objectives. The results of the annual analyses will be reported by Vertex in the study report.

The primary objectives of this study are to evaluate long-term safety, pregnancy outcomes, drug utilisation, and CF disease progression in patients treated with ivacaftor. Descriptive statistics will be presented for all endpoints.

All safety, pregnancy, and CF disease progression endpoints (Objectives 1, 2, and 3, respectively) will be compared between the Ivacaftor and Comparator Cohorts or between the Ivacaftor Pregnancy and Comparator Pregnancy Cohorts, as appropriate. Pregnancy outcomes will also be described for the Historical Cohort. Annual incidence rates will be calculated for safety outcomes. Crude relative risks or risk difference with 95% confidence intervals will be calculated for some outcomes, as appropriate. Statistical modelling with adjustment for confounders and effect modifiers may not be possible due to the likely sparse data. Identification of confounders and effect modifiers will be performed using stratified analyses. Each annual report will include the patient data collected during the previous calendar year (e.g., annual cross-sectional analysis). Longitudinal analyses will be included, as appropriate, in the final report.

Milestones

Milestone	Planned Date (CF Trust)	Planned Date (CF Foundation)
Start of data collection[a] (Ivacaftor and Comparator Cohorts)	June 2013[b]	June 2013[b]
End of data collection[a] (Ivacaftor and Comparator Cohorts)	June 2017	May 2017
Yearly reports	Annually from 2013 to 2016	Annually from 2013 to 2016
Final report of study results	December 2017	October 2017

[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.

[b] Data for the Historical Cohort will have been collected before ivacaftor was commercially available in the respective regions. The data extraction for the Historical Cohort will be conducted as part of the Year 1 Report activities.

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

Based on the marketing authorisation dates of ivacaftor in the United States (US; 31 January 2012) and European Union (EU; 23 July 2012), the milestones for data collection and analysis are different for the 2 patient registries, as indicated in the table below. Ivacaftor was first made commercially available in the US in February 2012. Ivacaftor has been commercially available (reimbursed) in the United Kingdom (UK) since January 2013. Each year, the Cystic Fibrosis (CF) Trust and CF Foundation create a data set for the patient registries. The process includes a data lock point of 31 December (US) and 31 January (UK) followed by a 3- to 4-month data entry and data cleaning period when sites are queried for data discrepancies. The final data made available to Vertex by the registries in April/May (US) and June (UK) each year will comprise patient data from the previous calendar year. Vertex's summary of the data provided and the preparation and submission of an annual study report are expected to be a 5- to 6-month process.

The milestones provided are based on protocol finalisation by June 2013.

Table 1 Study Milestones

	Planned Date	
Milestone	**CF Trust (UK)**	**CF Foundation (US)**
Start of data collection[a]	June 2013[b]	June 2013[b]
End of data collection[a]	June 2017	May 2017
Year 1 Report	December 2013[c]	December 2013[c]
Year 2 Report	December 2014	October 2014
Year 3 Report	December 2015	October 2015
Year 4 Report	December 2016	October 2016
Registration in EU PAS Register[d]	tbd	tbd
Final report of study results	December 2017	October 2017

CF: cystic fibrosis; EU PAS: European Union Post-authorisation Study; tbd: to be determined; UK: United Kingdom; US: United States.

[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.

[b] Data for the Historical Cohort will have been collected by the registries before ivacaftor was commercially available in the respective regions. The data extraction for the Historical Cohort will be conducted as part of the Year 1 Report activities.

[c] Based on the protocol finalisation date, the Year 1 Report will be completed later in the year than later annual reports (i.e., December instead of October).

[d] Study will be registered in EU PAS Register following Pharmacovigilance Risk Assessment Committee approval of final protocol and before study initiation.

Table 2 Objectives and Data to be Included in Each Annual Report

Annual Report	Objectives	Analyses
2013 (Year 1)	1. To evaluate the long-term safety of ivacaftor in patients with CF	Historical Cohort[a] (UK, US) Ivacaftor versus Comparator (US[b])
	2. To evaluate the outcomes of pregnancy in ivacaftor-treated patients	Historical Cohort[a] (UK, US) Ivacaftor Pregnancy Study versus Comparator Pregnancy Study (US[b])
	3. To evaluate the drug utilisation of ivacaftor	Drug Utilisation (UK, US)
	4. To evaluate CF disease progression in ivacaftor-treated patients	Data not available
2014 (Year 2)	1. To evaluate the long-term safety of ivacaftor in patients with CF	Ivacaftor versus Comparator (UK, US)
	2. To evaluate the outcomes of pregnancy in ivacaftor-treated patients	Ivacaftor Pregnancy Study versus Comparator Pregnancy Study (UK, US)
	3. To evaluate the drug utilisation of ivacaftor	Drug Utilisation (UK, US)
	4. To evaluate CF disease progression in ivacaftor-treated patients	Ivacaftor versus Comparator (UK, US)
2015 (Year 3)	1. To evaluate the long-term safety of ivacaftor in patients with CF	Ivacaftor versus Comparator (UK, US)
	2. To evaluate the outcomes of pregnancy in ivacaftor-treated patients	Ivacaftor Pregnancy Study versus Comparator Pregnancy Study (UK, US)
	3. To evaluate the drug utilisation of ivacaftor	Drug Utilisation (UK, US)
	4. To evaluate CF disease progression in ivacaftor-treated patients	Ivacaftor versus Comparator (UK, US)
2016 (Year 4)	1. To evaluate the long-term safety of ivacaftor in patients with CF	Ivacaftor versus Comparator (UK, US)
	2. To evaluate the outcomes of pregnancy in ivacaftor-treated patients	Ivacaftor Pregnancy Study versus Comparator Pregnancy Study (UK, US)
	3. To evaluate the drug utilisation of ivacaftor	Drug Utilisation (UK, US)
	4. To evaluate CF disease progression in ivacaftor-treated patients	Ivacaftor versus Comparator (UK, US)
2017 (Year 5)	1. To evaluate the long-term safety of ivacaftor in patients with CF	Ivacaftor versus Comparator (UK, US)
	2. To evaluate the outcomes of pregnancy in ivacaftor-treated patients	Ivacaftor Pregnancy Study versus Comparator Pregnancy Study (UK, US)
	3. To evaluate the drug utilisation of ivacaftor	Drug Utilisation (UK, US)
	4. To evaluate CF disease progression in ivacaftor-treated patients	Ivacaftor versus Comparator (UK, US)

CF: cystic fibrosis; UK: United Kingdom; US: United States.

Note: The annual report of each year provides patient data from the previous year.

[a] Data extraction for the Historical Cohort (2008 patient data) will be conducted as part of the Year 1 Report activities. Stratification will be performed as appropriate, for example, to identify outcomes for patients younger than 6 years of age.

[b] The CF Trust Patient Registry did not collect data on ivacaftor use until 2013. Therefore, no UK data for the Ivacaftor versus Comparator Cohort comparison are expected in the Year 1 Report.

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. Cystic fibrosis affects approximately 70,000 individuals worldwide,[3] with approximately 30,000 individuals in the US, 36,000 individuals in the EU,[4] 3800 individuals in Canada,[5] and 3000 individuals in Australia.[6]

Cystic fibrosis 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.[7] CFTR is an epithelial chloride channel responsible for helping to regulate salt and water absorption and secretion in various tissues.[8] At present, there is no cure for CF, and despite adjunctive treatments with nutritional supplements, antibiotics, and mucolytics,[9] the median predicted age of survival for a person born today with CF is approximately 40 years of age.[2,10]

Over 1800 mutations in the *CFTR* gene have been identified.[11] Of these mutations, over 1300 are potentially CF-causing[12]; they result in either a diminished level of CFTR in the apical membrane or a decreased ability to transport anions such as chloride or bicarbonate. The most frequent mutation is an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein, commonly referred to as F508del.[2] More than 88% of patients with CF in the US have at least 1 copy of *F508del-CFTR*, with about half of those being homozygous for this mutation. Whilst the predominant effect of the F508del mutation is a severe decrease in the amount of CFTR trafficked to the cell surface, the mutation also results in defective CFTR channel gating.[2] A defect in channel opening is also a characteristic of G551D-CFTR (a missense mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue),[13] but unlike F508del-CFTR, G551D-CFTR is delivered to the cell surface in normal amounts. *CFTR* gene mutations, like *G551D*, in which the primary defect results in CFTR protein with reduced channel opening, are known as CFTR gating mutations. *G551D* is the most common CF-causing gating mutation. Mutations in *CFTR* have been classified on the basis of the molecular consequences (functional impact) to the genetic mutation into 5 classes described in Table 3.[14]

Table 3 Classes of *CFTR* Mutations

Parameter	Class I	Class II	Class III	Class IV	Class V
Functional impact	Little or no CFTR synthesis	Incomplete CFTR processing	Defective CFTR gating	Defective chloride ion conductance	Reduced CFTR synthesis
Examples[a]	*G542X* *W1282X*	*F508del* *N1303K*	*G551D* *S1255P*	*R334W* *R347P*	*2789+5G→A* *A455E*

Sources: McKone et al.,[14] Kerem and Kerem,[15] Rowe et al.,[16] and MacDonald et al.[17]
CFTR: cystic fibrosis transmembrane conductance regulator gene.
[a] Representative mutations for each class are provided.

One approach to increasing the level of chloride transport through the CFTR channels is to treat with a potentiator, a compound that increases the duration of channel opening whilst maintaining the normal regulation by cyclic-adenosine monophosphate-dependent phosphorylation.[18]

Ivacaftor (formerly VX-770), a compound developed by Vertex Pharmaceuticals Incorporated (Vertex), is classified as a CFTR potentiator. Ivacaftor (Kalydeco™; 150-mg tablets) was approved in the US and the EU in 2012 for the treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene. Ivacaftor is an orally bioavailable small molecule CFTR potentiator that targets the underlying defect in CF. As such, ivacaftor is a member of a new class of drugs—CFTR modulators—that provide a new therapeutic approach to the treatment of CF. Ivacaftor is the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF.

7.2 Rationale

Results from the development programme of ivacaftor showed that ivacaftor was well tolerated, with the most common adverse events being typical manifestations of CF disease. In subjects who have a *G551D* mutation in at least 1 allele of the *CFTR* gene, the most common adverse reactions in subjects who received ivacaftor include abdominal pain, diarrhoea, dizziness, rash, upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis), headache, and bacteria in sputum. The most common serious adverse events in subjects receiving ivacaftor were CF exacerbations and haemoptysis, both of which are common manifestations of CF. Elevations of transaminases occurred in a small number of subjects in both the placebo and ivacaftor groups with similar incidence; the role of ivacaftor in contributing to transaminase elevations is uncertain, although data do not support an association. Based on the clinical safety database, the Risk Management Plan (RMP) identified several important potential risks, including the effect of long-term ivacaftor treatment on pulmonary exacerbation and bacterial sputum colonisation; off-label use (i.e., ivacaftor treatment in patients <6 years of age and patients who do not have the *G551D* mutation in the *CFTR* gene); effect of ivacaftor treatment in patients with forced expiratory volume in 1 second (FEV_1) <40% predicted value, cardiac disease, or hepatic impairment; and effect of ivacaftor treatment in pregnant or lactating women (see Kalydeco EU RMP).

Safety concerns identified in nonclinical studies that are not adequately addressed by clinical data include hepatotoxicity (repeat-dose toxicity studies in rats and mice), presence of ivacaftor in breast milk (radiolabelled ivacaftor study in pregnant and lactating rats), and cataracts (lens opacities identified in juvenile toxicology study in rats) (see Kalydeco EU RMP).

Efficacy results from the development programme showed that ivacaftor treatment targets the underlying pathophysiology of CF and has a broad array of benefits for subjects who have the *G551D* mutation in the *CFTR* gene. The Phase 3 studies showed that treatment with ivacaftor has systemic benefit, including substantial and durable improvements in pulmonary and extrapulmonary measures, with corresponding sustained improvements in CFTR function. The treatment effect in FEV_1 favored ivacaftor across all subgroups analysed.

Improvements in FEV_1 were persistent to 96 weeks of ivacaftor treatment. Notably, the efficacy of ivacaftor was observed whilst subjects continued on their prescribed therapies for CF. CF disease progression, as measured by pulmonary function or clinical signs, has not been studied beyond the ivacaftor clinical development programme. Therefore, there is a need to better understand the long-term effects of ivacaftor on pulmonary function as well as clinical signs of disease such as cystic fibrosis related diabetes (CFRD). This study will provide additional analyses on disease progression for up to 5 years.

Ivacaftor is intended for chronic, potentially lifelong use. Understanding of the long-term effects will be informative to patients and their parents, prescribers, and payers. Therefore, this post-authorisation safety study (PASS) will evaluate the identified potential risks of ivacaftor and CF disease progression in patients with CF who are treated with ivacaftor using observational cohorts of patients receiving ivacaftor in a "real-world" setting. Additionally, ivacaftor is indicated for patients 6 years of age and older who have the *G551D* mutation in the *CFTR* gene, without limitations on the patients' lung function. Hence, the patient population in this study will also include patients with minimal lung disease, a group on which there were limited data from the development programme of ivacaftor. The broader ivacaftor-exposed population available in this study will provide an opportunity to study CF disease progression as determined by pulmonary function and CF complications such as CFRD.

In the UK, the CF Trust has established a CF patient registry that states its main objective as to drive up standards of clinical care for patients with CF throughout the United Kingdom. As reported in the 2010 annual data report, the CF registry has enrolled over 9000 patients with CF, including 432 patients whose recorded genotype data have the *G551D* mutation.[1]

In the US, the CF Foundation has established the CF Patient Registry that tracks the treatments and health of people with CF across the United States. As of the 2010 Annual Data Report, data have been collected on over 26,000 patients. Amongst patients with genotype reported, 1035 have the *G551D* mutation.[2]

In both patient registries, data collection is encounter-based with a comprehensive annual assessment of healthcare received and health outcomes. The Ivacaftor Long-term Safety Study, a PASS, will consist of analyses of safety and CF disease progression outcomes for ivacaftor-treated and comparator patients enrolled in the CF Trust and the CF Foundation patient registries.

8 RESEARCH QUESTIONS AND OBJECTIVES

8.1 Primary Objectives

1. To evaluate the long-term safety of ivacaftor in patients with CF
2. To evaluate outcomes of pregnancy in ivacaftor-treated patients
3. To evaluate the drug utilisation of ivacaftor
4. To evaluate CF disease progression in ivacaftor-treated patients

The comparisons to be made for each objective are described in Section 9.3.4 (Table 5).

8.2 Secondary Objectives

8.2.1 Secondary Objectives for Primary Objective 1

1. To evaluate the long-term safety of ivacaftor amongst patients in the following subgroups:
   - Patients between 6 and 11 years of age
   - Patients with FEV_1 <40% predicted value
   - Patients with cardiac disease
   - Patients with moderate or severe hepatic impairment
2. To evaluate pulmonary exacerbations and bacterial sputum colonisation with long-term ivacaftor treatment

8.2.2 Secondary Objective for Primary Objective 2

To measure the frequency of pregnancy in ivacaftor-treated patients

8.2.3 Secondary Objectives for Primary Objective 3

Off-label use amongst patients within the following subgroups:

- Children less than 6 years of age
- Patients with Class III, non-*G551D-CFTR* mutations
- Patients with non-Class III mutations

8.2.4 Secondary Objectives for Primary Objective 4

To evaluate the effect of ivacaftor on CF disease progression, as measured by

- CF lung disease severity, based on pulmonary function (e.g., percent predicted FEV_1)
- Clinical signs of CF disease progression (e.g., death, transplantation, CFRD, distal intestinal obstruction syndrome [DIOS])
- Change in lung function over time

8.3 Prior Hypotheses

The purpose of this study is to perform analyses that will inform us on the long-term safety of ivacaftor use in patients with CF. Given the known safety profile of ivacaftor, this study will further characterise the safety of chronic ivacaftor treatment in real-life use and provide descriptive analyses on specified safety and CF disease progression outcomes using observational data. These analyses will be used for hypothesis generation for safety issues that warrant future study. Therefore, no prior hypotheses are proposed for the primary objectives. Prior hypothesis is provided for specific secondary objectives, although the study may be underpowered to detect any differences:

- Pulmonary exacerbations: similar or lower incidence in the Ivacaftor Cohort than the Comparator Cohort and previously observed in the pivotal Phase 3 studies (as described in the Summary of Product Characteristics [SmPC])
- Adverse drug reactions (as listed in the SmPC): similar or lower incidence in the Ivacaftor Cohort than the Comparator Cohort and previously observed in the pivotal Phase 3 studies (as described in the SmPC)
- Serious adverse events and adverse events leading to withdrawal of ivacaftor: similar or lower incidence in the Ivacaftor Cohort than the Comparator Cohort (CF Trust data only).

9 RESEARCH METHODS

9.1 Study Design

To evaluate the long-term safety and CF disease progression in patients with CF who are treated with ivacaftor, this PASS comprises observational cohorts of patients receiving ivacaftor who are in the CF Trust and the CF Foundation patient registries. Existing CF registries provide an established source to obtain long-term safety in a real-life setting for analysis. The CF Trust and CF Foundation patient registries provide the ideal source to obtain long-term safety information because the data collected are extensive and consistent with one another. In addition, the patients with CF from the CF Trust and the CF Foundation patient registries encompass a majority of the patients in the indicated population. The encounter-based patient data collected by the registries constitute secondary data; no primary data will be collected for this study. Each registry will conduct an annual analysis of data accumulated in the previous year.

Given the global prevalence of CF, the limited size of the CF population indicated for treatment with ivacaftor (i.e., *G551D* mutation), and the availability of national registries of patients with CF that currently collect data on treatment patterns, safety, and pulmonary function outcomes of patients with CF, Vertex decided to work with the patient registries in the UK and in the US to meet the study objectives. This decision was made based on feedback from CF healthcare providers who indicated that a separate ivacaftor registry would be burdensome to patients and staff at CF care centres. In addition, the patients followed in these registries are expected to be representative of patients with CF with the *G551D* mutation globally. However, additional sources of patient data from the EU are under investigation for inclusion into the drug utilisation objective (Study Objective 3 [Section 8.1]).

Observational or noninterventional study design is the preferred method used to understand the safety of products in the "real-world" setting and allows for data collection of outcomes without influencing treatment patterns. Once market authorisation is achieved, it is expected that a broader patient population will be exposed to the drug compared to the population exposed in the clinical development programme. The observational design allows for the study of outcomes in the newly exposed population and, because of the availability of historical data for patients enrolled in the registries, previously exposed patients. With this design, we estimate that a subset of patients who were exposed to ivacaftor during clinical development and continue to be treated with ivacaftor will have exposure durations of greater than 5 years when analysed for the annual reports.

9.1.1 Study Population

The Ivacaftor Cohort will include all patients who have been treated with ivacaftor and are enrolled in the CF Trust or CF Foundation patient registries. The Comparator Cohort will include patients who have never been exposed to ivacaftor and are matched on age group, *CFTR* genotype class, and sex (see Section 9.2.4) to patients in the Ivacaftor Cohort.

The Ivacaftor Pregnancy Study Cohort will include all female patients who have ivacaftor exposure in the analysis year and are enrolled in the CF Trust or CF Foundation patient registries. The Comparator Pregnancy Study Cohort will include female patients who have never been exposed to ivacaftor and are matched on *CFTR* genotype class to patients in the Ivacaftor Pregnancy Study Cohort (see Section 9.2.4).

The Comparator and Comparator Pregnancy Study Cohorts will be identified for each registry's Ivacaftor and Ivacaftor Pregnancy Study Cohorts, respectively, at a ratio of m:1, where m is the maximum number of matches available.

The Historical Cohort will include patients who have the *G551D-CFTR* mutation, were enrolled in the patient registries before ivacaftor was available in clinical studies and commercially in the US and the UK (i.e., 2008), and were never exposed to ivacaftor.

The Drug Utilisation Cohort will include all patients who have ever been treated with ivacaftor.

9.1.2 Inclusion and Exclusion Criteria

9.1.2.1 Ivacaftor Cohort

Inclusion Criteria

1. Patients with CF in the CF Trust or the CF Foundation patient registries
2. Patients treated with ivacaftor

Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

9.1.2.2 Comparator Cohort

Inclusion Criteria

1. Patients with CF in the CF Trust or the CF Foundation patient registries

2. Patients with no evidence of ivacaftor exposure (current or past)
3. Patients matched to patients in the Ivacaftor Cohort on age group, *CFTR* genotype class, and sex (see Section 9.2.4 for matching criteria)

Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

9.1.2.3 Historical Cohort

Inclusion Criteria

1. Patients with CF in the CF Trust or the CF Foundation patient registries
2. Patients with the *G551D-CFTR* mutation
3. Patients with no evidence of ivacaftor exposure before ivacaftor was available commercially

Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

9.1.2.4 Ivacaftor Pregnancy Study Cohort

Inclusion Criteria

1. Female patients with CF in the CF Trust or the CF Foundation patient registries
2. Patients 13 years of age or older
3. Patients treated with ivacaftor

Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

9.1.2.5 Comparator Pregnancy Study Cohort

Inclusion Criteria

1. Female patients with CF in the CF Trust or the CF Foundation patient registries
2. Patients 13 years of age or older
3. Patients with no evidence of ivacaftor exposure (current or past)
4. Patients matched on *CFTR* genotype class to patients in the Ivacaftor Pregnancy Study Cohort

Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

9.1.2.6 Drug Utilisation Cohort

Inclusion Criteria

1. Patients with CF in the CF Trust or the CF Foundation patient registries
2. Patients with current ivacaftor exposure

Exclusion Criterion

1. Participation in an interventional study during the analysis period (if available)

9.2 Setting

9.2.1 Cystic Fibrosis Trust and Cystic Fibrosis Foundation

Patient registries established by the CF Trust and the CF Foundation will be used for this study. These registries are the largest in the geographic regions covered by the current study, representing approximately 9400 of 36,000 patients with CF in the EU and approximately 26,000 of 30,000 patients with CF in the US.[1,2] The Ivacaftor Long-term Safety Study is an analysis of data collected in these patient registries. These registries are disease registries of observational cohort study design.

The CF Trust Patient Registry is an anonymised database of all those with CF in the UK. This database is maintained by the CF Trust. It is an invaluable tool that is used by the CF Trust to identify patterns and anomalies in CF care and outcomes across the UK.[19]

The CF Foundation Patient Registry tracks the treatments and health of people with CF across the US. Information is collected every year on patients who receive care at CF Foundation-accredited care centres and agree to participate in the registry.[2]

In both registries, all patients participate in standard encounter-based data collection including annual assessments for death, organ transplantation, hospitalisations, complications, pulmonary exacerbations, respiratory microbiology, pregnancy, and pulmonary function. Investigators at CF care centres enter data for their enrolled patients with CF into the registry databases. In both registries, investigators are physicians at certified CF care centres. Data collection forms were developed to 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 data elements collected are provided in standard terms for diagnoses and treatments and are considered adjudicated diagnoses.

Efforts have been made to provide consistency of care to patients with CF throughout the world. These efforts include treatment guidelines created and maintained by the European Cystic Fibrosis Society (ECFS) and the CF Foundation.[20,21] Therefore, we are confident that the patient registries in the UK and the US are representative of patients with CF globally.

9.2.2 Other Patient Registries

At the request of the Pharmacovigilance Risk Assessment Committee, other EU patient registries were considered for this study. A feasibility assessment for the inclusion of these registries is provided in Annex 3: Additional Information.

9.2.3 Study Cohorts

Patients from the patient registries will be categorised into 6 cohorts.

1. The Ivacaftor Cohort will include all ivacaftor-treated patients enrolled in the CF Trust or CF Foundation patient registries, regardless of age, *CFTR* genotype, or pulmonary function.

2. The Comparator Cohort will include patients who are not receiving and have never received ivacaftor and are a match on age group, *CFTR* genotype class, and sex to patients in the Ivacaftor Cohort. Based on the mechanism of action of ivacaftor and the availability of genetic testing, it is expected that most patients with *G551D-CFTR* mutation will be exposed to ivacaftor during the study period, making it challenging to identify a comparator cohort of patients with CF with the *G551D-CFTR* mutation who are not exposed to ivacaftor. Therefore, patients in the Comparator Cohort will be matched on *CFTR* genotype class based on the functional classification of *CFTR* alleles.[14,22]
3. The Historical Cohort will include patients who have the *G551D-CFTR* mutation, were enrolled in the patient registries in 2008 (before ivacaftor was available in clinical studies and commercially in the UK and the US), and have no evidence of exposure to ivacaftor.
4. The Ivacaftor Pregnancy Study Cohort will include all female patients 13 years of age or older who were enrolled in the patient registries and were treated with ivacaftor.
5. The Comparator Pregnancy Study Cohort will include female patients who are not receiving and have never received ivacaftor and are a match on *CFTR* genotype class to patients in the Ivacaftor Pregnancy Cohort.
6. The Drug Utilisation Cohort will include all patients who were enrolled in the patient registries with evidence of ivacaftor exposure.

9.2.4 Comparator Matching

For analyses of safety outcomes and CF disease progression (Objectives 1 and 4), patients in the Comparator Cohort will be matched to patients in the Ivacaftor Cohort on age group, then *CFTR* genotype class, and then, whenever possible, sex, to account for differences in health outcomes during the progression of CF and known differences in health outcomes for male and female patients.[23-27]

For analyses of pregnancy outcomes (Objective 2), patients in the Comparator Pregnancy Study Cohort (female patients only) will be matched to patients in the Ivacaftor Pregnancy Study Cohort on *CFTR* genotype class; no other matching criterion is used in order to maximise the number of potential matches for an event (pregnancy) expected to have low incidence compared to other safety outcomes.

Age

Age matches will be made based on an age bracket within specific age group categories.

- Patients 0 to 11 years of age (inclusive) will have a bracket of -2 years.
- Patients 12 to 20 years of age (inclusive) will have a bracket of ±2 years.
- Patients older than 20 years of age will have a bracket of ±5 years.
- Age group categories will be 0 to 2, 3 to 5, 6 to 8, 9 to 12, 13 to 17, 18 to 20, 21 to 25, 26 to 30, 31 to 35, 36 to 40, and >40 years.

For example, a 16-year-old Ivacaftor Cohort patient will be matched to patients in the Comparator Cohort within the bracket of ±2 years of age (i.e., 14 to 18 years of age), as

limited by the age group category of 13 to 17 years of age (i.e., final age match to patients 14 to 17 years of age). A 21-year-old Ivacaftor Cohort patient will be matched to patients in the Comparator Cohort within the bracket of ±5 years of age (i.e., 16 to 26 years of age), as limited by the age group category of 21 to 25 years of age (i.e., final age match to patients 21 to 25 years of age).

Age group categories may be collapsed to increase matching when nonexposed patients are not available for matching. These age groups were chosen based on the age-related decline in pulmonary function in patients with CF.[28,29]

CFTR genotype class

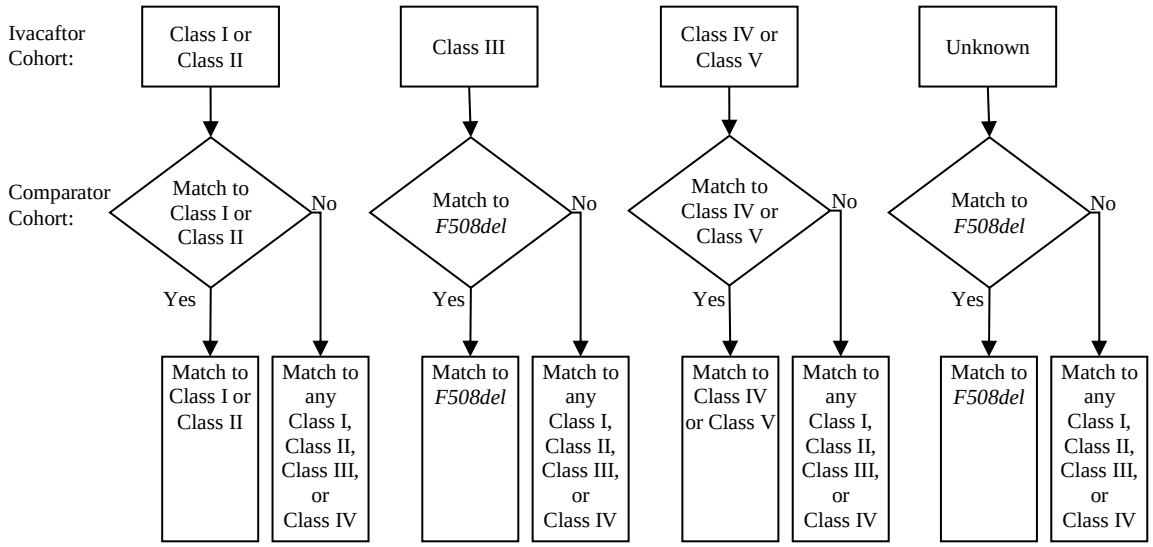
The Class III *CFTR* mutations include *G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G970R*, *G1244E*, *S1251N*, *S1255P*, *G1349D*, and *R560T* (see also RMP).[14] Because of the low prevalence of Class III mutations (<5% overall with approximately 1% representing non-*G551D* mutations), it will not be possible to match patients with the *G551D* mutation to patients with other Class III mutations. The following matching scheme for genotype will be implemented.

- Any Class III *CFTR* allele will be matched to *F508del*, a mutation in a different class (Class II) but of similar phenotype (similar sweat chloride levels, FEV_1, forced vital capacity, height, weight, pancreatic sufficiency, and incidence of *Pseudomonas aeruginosa* colonisation).[14,22] For example, a patient with *CFTR* alleles of *G551D/F508del* will be matched to a patient with *CFTR* alleles of *F508del/F508del*.
- Alleles in *CFTR* Classes I and II will be matched to Class I or II; alleles in *CFTR* Classes IV and V will be match to Class IV or V.

This scheme will allow for patients with a second allele associated with less severe phenotype (e.g., Class IV or V) to be matched to a patient with a similar genotype and not a more severe class (e.g., Class I to III). Patients with an allele of unknown genotype (meaning mutation has not yet been identified) or a mutation of unknown mutation class will be matched to *F508del*.

The genotype matching algorithm is provided in Figure 1.

Figure 1 Genotype Matching Algorithm



9.2.5 Other Matching Considerations

Given the limited size of the CF population, the Comparator and Comparator Pregnancy Cohorts will not be matched for other measures of disease severity (e.g., percent predicted FEV_1, *Pseudomonas aeruginosa* infection) due to concerns about availability of adequate patients for matching. However, measures of disease severity will be included as stratification variables and as covariates for adjustment, as necessary.

The Historical Cohort will include patients with a *G551D-CFTR* mutation who were in the patient registries in 2008. These patients were chosen because they represent the best match to ivacaftor-treated patients in 2012 and later because they match the indicated patient population based on the approved product labelling. The Historical Cohort will include patients of all ages and will be stratified to identify outcomes for patients younger than 6 years of age (for the potential off-label population). The year 2008 was chosen because starting in 2009, ivacaftor clinical studies were actively enrolling in the UK and US. A 1-year window was selected to match the window for safety outcome analysis in the Ivacaftor and Comparator Cohorts. The Historical Cohort will be analysed once for Objectives 1 and 2 for all stratification variables. If additional analyses are identified during the conduct of the study, the Historical Cohort will be available for analysis.

9.2.6 Annual Reporting

To meet the study objectives, data for outcomes will be analysed separately for each registry for 5 years. All enrolled patients exposed to ivacaftor will be included in the Ivacaftor Cohort, and patients not exposed to ivacaftor and matched for age group, *CFTR* mutation class, and sex, as appropriate, will be included in the Comparator Cohort in the study analyses in each annual report. Each annual report will include the data collected during the previous calendar year. Longitudinal analyses will be included in the final report. The

Historical Cohort will provide an estimate of rates for variables supporting Objectives 1 and 2 and be included in the first yearly report.

9.3 Variables

All variables for study endpoints are collected in prespecified data collection forms. For example, specific diagnoses are captured as data elements rather than as a collection of information from which a diagnosis would be made. Adjudication is done by the governing committees of the patient registries. 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. Because verbatim terms are not reported and forms contain adjudicated diagnoses, the data are inherently coded. Each registry employs its own data entry guideline rather than use external coding dictionaries.

The CF Trust and CF Foundation patient registries employ data collection instructions and rigorous data cleaning procedures to provide robust data sets for the analysis of ivacaftor safety, drug utilisation, and CF disease progression. The principal investigators of this protocol are both physicians with expertise in CF, familiar with the current standards for treating patients with CF, as well as the data quality process of their respective registries. Therefore, an external expert committee for validation of diagnoses is not planned.

The CF Trust and CF Foundation independently determine the data to be collected; thus, the specific variables included in the analyses for this study are not necessarily identical. Types of variables important for this analysis include exposure, outcomes, and stratification variables. Stratification variables will be explored to identify confounders and effect modifiers. Data are collected for each patient registry; therefore, variables are described separately (Sections 9.3.1 and 9.3.2). Table 4 provides a comparison of the variables to be collected.

Table 4 Comparison of Variables Collected by the Patient Registries

Variables	CF Trust (UK)	CF Foundation (US)
Exposure	start/stop (reason)	yes (150 mg/other)/no
Prior ivacaftor exposure	Derived based on start date before January 2013	Derived based on ivacaftor exposure in 2012
Death	date; cause (respiratory/ cardiorespiratory, liver disease, trauma, suicide, transplant-related, other)	date; cause (respiratory/ cardiorespiratory, liver disease, trauma, suicide, transplant-related, other, unknown)
Organ transplantation	yes (lung, other)/no	yes (lung, liver, kidney, other)/no
Hospitalisation	start date of hospitalisation for pulmonary exacerbation	start date (any hospitalisation); reason (pulmonary exacerbation, pulmonary complication, GI complication, transplant-related, sinus infection, non-transplant surgery, other)
CF complications	see Section 9.3.1.2	see Section 9.3.2.2
Pulmonary exacerbations and respiratory microbiology[a]	yes/no; respiratory microbiology	yes/no; respiratory microbiology

Table 4 Comparison of Variables Collected by the Patient Registries

Variables	CF Trust (UK)	CF Foundation (US)
Pregnancy	pregnancy occurrence/outcome/ undelivered/unknown; gestational age; presence of congenital anomalies at birth; only for female patients 13 years of age and older	pregnancy occurrence/outcome/ undelivered/unknown; only for female patients
Serious safety outcomes	combination of death, organ transplantations, hospitalisations, and selected CF complications	combination of death, organ transplantations, hospitalisations, and selected CF complications
Pulmonary function tests[b]	FEV_1 (L), best FEV_1(L), FVC (L), $FEF_{25\%-75\%}$ (L) during last period, unable to perform test, not done	FEV_1 (L), FVC (L), $FEF_{25\%-75\%}$ (L), unable to perform test
Cardiac disease	as reported in CF complication	as reported in reason for hospitalisation or CF complications
Hepatic impairment	reported as liver disease with portal hypertension	reported as liver disease with complications

CF: cystic fibrosis; $FEF_{25\%-75\%}$: forced midexpiratory flow; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GI: gastrointestinal; UK: United Kingdom; US: United States.

[a] Whilst the specific respiratory microbiology variables collected by the CF Trust and the CF Foundation differ, efforts will be made to create general categories for the analyses. Details will be provided in the statistical analysis plan.

[b] Percent predicted FEV_1 will be calculated based on the equations of Hankinson et al.[30] or Wang et al.[31] The Hankinson standard will be used for male patients 18 years and older and female patients 16 years and older. The Wang standard will be used for male patients aged 6 to 17 years and for female patients aged 6 to 15 years.

9.3.1 Variables for Cystic Fibrosis Trust Patient Registry (UK)

9.3.1.1 Exposure

Ivacaftor exposure will be determined by first evidence of ivacaftor treatment and patients will remain exposed until there is evidence of discontinuation of ivacaftor in the patient registry database. Because start and stop dates are available, ivacaftor exposure will be calculated in days. When start and stop dates are not available due to missing data, 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. Ivacaftor exposure will be categorised into the meaningful groups based on the distribution of exposure, such as <1 year, 1 to <2 years, and ≥2 years. For patients who discontinue treatment with ivacaftor, reason for discontinuation (lack of benefit, side effect, other) will be described.

9.3.1.2 Outcomes

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

Organ transplantations will be defined if there is evidence of an organ transplantation. Type of transplant will include lung and other.

Hospitalisations will be defined if there is evidence of a start date for a hospitalisation for a pulmonary exacerbation.

CF complications include the following:

- allergic bronchial pulmonary aspergillosis (ABPA)
- absence of vas deferens
- arthritis
- arthropathy
- asthma
- bone fracture
- cancer confirmed by histology
- cardiac disease
- CFRD
- chronic *P aeruginosa* colonisation
- chronic *Staphylococcus aureus* colonisation
- cirrhosis with portal hypertension
- cirrhosis with no portal hypertension
- depression
- DIOS
- fibrosing colonopathy/ colonic stricture
- gallbladder disease requiring surgery
- gastroesophageal reflux disease (GERD)
- gastrointestinal (GI) bleed (non-variceal) requiring hospitalisation
- GI bleed (variceal) requiring hospitalisation
- Haemoptysis
- Hearing loss
- hypertension
- kidney stones
- liver disease, non-cirrhosis
- liver enzymes elevated
- nasal polyps requiring surgery
- nontuberculous mycobacteria (NTM) infection (not requiring treatment)
- NTM infection (requiring treatment)
- osteopenia
- osteoporosis
- pancreatitis
- peptic ulcer disease
- pneumothorax requiring chest tube
- port inserted or replaced
- rectal prolapse
- renal failure requiring dialysis
- septicaemia
- sinus disease
- other, specify including cataract

Pulmonary exacerbations will be defined by evidence of a CF care episode or hospitalisation with reason pulmonary exacerbation. Respiratory microbiology will include patients with a bacterial culture and evidence of chronic colonisation with *Staphylococcus aureus*, chronic *P aeruginosa*, intermittent *P aeruginosa*, *Burkholderia*, methicillin-resistant *Staphylococcus aureus*, and *Haemophilus influenzae*.

Serious safety outcomes will be defined by combining death, organ transplantations, hospitalisations, and selected CF complications.

Pregnancy will be defined if there is evidence of pregnancy in the database. Pregnancy data are collected for female patients 13 years of age and older. Outcomes include live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown. In addition, gestational age and congenital anomalies will be included.

Cardiac disease will be defined by specification of cardiac disease as a CF complication.

CF lung disease severity will be defined if there is evidence of pulmonary function test results in the database. Absolute measures (in litres) for FEV_1 (best FEV_1 during last period) are collected. Percent predicted FEV_1 will be calculated based on the Hankinson[30] or Wang[31] equations (see Section 9.3.4.4).

Clinical signs of CF disease progression will be defined by outcomes previously specified, including death, organ transplantation, and selected CF complications (CFRD and DIOS).

Change in lung function over time will be defined by pulmonary function test results over the years in the analysis. Absolute measures (in litres) for FEV_1, forced vital capacity (FVC) and forced midexpiratory flow ($FEF_{25\%-75\%}$) (best values during last period) are collected. Percent predicted values will be calculated based on the equations of Hankinson et al.[30] or Wang et al.[31] (see Section 9.3.4.4).

9.3.1.3 Analysis Variables

Age will be defined using date of birth.

Sex will be defined as reported in database.

Genotype will be defined for each allele and will be categorised by *CFTR* mutation class.

Baseline percent predicted FEV_1 will be defined by most recent value obtained before initiating ivacaftor in the Ivacaftor Cohort; percent predicted FEV_1 will be date-matched for the Comparator Cohort. Standardised equations (those of Hankinson et al.[30] or Wang et al.[31] [see Section 9.3.4.4]) will be used to calculate percent predicted FEV_1 and will be specified in the statistical analysis plan (see Stand-alone Document 4 listed in Annex 1. List of Stand-alone Documents). Analysis of FVC and $FEF_{25\%-75\%}$ will also be specified in the statistical analysis plan. Pulmonary function test results are available for 95% of patients in the registry. One pulmonary function measure is collected per calendar year for each patient.

Cardiac disease will be defined by evidence of cardiac disease in specified CF complications.

Hepatic impairment will be defined by "liver disease, non-cirrhosis".

9.3.2 Variables for Cystic Fibrosis Foundation Patient Registry (US)

9.3.2.1 Exposure

Ivacaftor exposure will be determined by first evidence of ivacaftor treatment and patients will remain exposed until there is evidence of discontinuation of ivacaftor in the patient registry database. Because 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: the date of the first encounter with evidence of ivacaftor exposure will be used as the start date. Patients will be identified as exposed to ivacaftor until a medications form is completed where ivacaftor treatment is not reported. The ivacaftor stop date will be the encounter date where exposure is not indicated. Ivacaftor exposure will be categorised into the meaningful groups based on the distribution of exposure, such as <1 year, 1 to <2 years, and ≥2 years.

9.3.2.2 Outcomes

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

Organ transplantations will be defined if there is evidence of an organ transplantation. Type of transplant will include lung, liver, kidney, and other.

Hospitalisations will be defined if there is evidence of a start date for a hospitalisation. Reason for hospitalisation includes pulmonary exacerbation, pulmonary complication, GI complication, transplant-related, sinus infection, non-transplant surgery, other.

CF complications include the following:

- CFRD status (impaired glucose tolerance, CFRD with or without fasting hyperglycaemia, CFRD complications [retinopathy, microalbuminuria, chronic renal insufficiency, chronic renal failure requiring dialysis, peripheral neuropathy])
- Hepatobiliary (gall stones, gall stones requiring surgery, liver disease [cirrhosis], cirrhosis complications [oesophageal varices, gastric varices, GI bleed, splenomegaly, hypersplenism, ascites], liver disease [noncirrhosis], hepatic steatosis, liver disease [other])
- Bone/Joints (arthritis/arthropathy, bone fracture, osteopenia, osteoporosis)
- Pulmonary (ABPA, asthma, haemoptysis-massive, pneumothorax requiring chest tube)
- Gastrointestinal (DIOS, fibrosing colonopathy/colonic stricture, GERD, GI bleed [non-variceal] requiring hospitalisation, pancreatitis, peptic ulcer disease, rectal prolapse)
- Other (absence of vas deferens, anxiety disorder, cancer confirmed by histology, depression, hearing loss, hypertension, kidney stones, nasal polyps requiring surgery, renal failure requiring dialysis [cause other than CFRD], sinus disease [symptomatic], other [specify including cataract])

Pulmonary exacerbations will be defined by evidence of a CF care episode with reason pulmonary exacerbation. Respiratory microbiology will include patients with a bacterial culture and evidence of *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Burkholderia*, fungal/yeast, other.

Serious safety outcomes will be defined by combining death, organ transplantations, hospitalisations, and selected CF complications.

Pregnancy will be defined if there is evidence of pregnancy in the database. Outcomes include live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown. Note that the CF Foundation Patient Registry does not have a variable of "congenital abnormality" for pregnancy outcome; however, as part of routine pharmacovigilance activities, Vertex collects unsolicited reports of pregnancy using the Pregnancy Safety Information Collection Form (see Stand-alone Document 4 listed in Annex 1. List of Stand-alone Documents). Matching of pregnancy cases between the unsolicited reports and the CF Foundation Patient Registry data will be as thorough as

possible, with considerations for the anonymous nature of the registry data and for patients from the spontaneous reports who may not be in the registry and vice versa.

Cardiac disease will be defined by specification of cardiac disease as a reason for hospitalisation or as a CF complication.

CF lung disease severity will be defined if there is evidence of pulmonary function test results in the database. Absolute measures (in litres) for FEV_1, best FEV_1 during last period, FVC, and $FEF_{25\%-75\%}$ are collected. Percent predicted values will be calculated based on the equations of Hankinson et al.[30] or Wang et al.[31] (see Section 9.3.4.4). Pulmonary function data are collected at each encounter. On average, there are 5 pulmonary function measures in a calendar year for each patient. In the US, the standard of care for CF includes quarterly office visits to the CF care centre. Best FEV_1 is identified per calendar quarter for each patient.

Clinical signs of CF disease progression will be defined by outcomes previously specified, including death, organ transplantation, and selected CF complications (e.g., CFRD and DIOS).

Change in lung function over time will be defined by pulmonary function test results over the years in the analysis. Absolute measures (in litres) for FEV_1 (current FEV_1 at each encounter) are collected. Percent predicted FEV_1 will be calculated based on the equations of Hankinson et al.[30] or Wang et al.[31] (see Section 9.3.4.4).

9.3.2.3 Analysis Variables

Age will be defined using date of birth.

Sex will be defined as reported in database.

Genotype will be defined for each allele and will be categorised by *CFTR* mutation class.[14,22]

Baseline percent predicted FEV_1 will be defined by most recent value obtained before initiating ivacaftor in the Ivacaftor Cohort; percent predicted FEV_1 will be matched to the most recent available value by calendar date for the Comparator Cohort. Standardised equations (those of Hankinson et al.[30] or Wang et al.[31] [see Section 9.3.4.4]) will be used to calculate percent predicted FEV_1 and will be specified in the statistical analysis plan (see Stand-alone Document 4 listed in Annex 1. List of Stand-alone Documents). Analysis of FVC and $FEF_{25\%-75\%}$ will also be specified in the statistical analysis plan.

Cardiac disease will be defined by evidence of cardiac disease in reason for hospitalisation or in specified CF complications.

Hepatic impairment will be defined by liver disease with complications (e.g., cirrhosis complications: oesophageal varices, gastric varices, GI bleed, splenomegaly, hypersplenism, ascites).

9.3.3 Study Endpoints

1. Safety
    - Death
    - Organ transplantations

- Hospitalisations
- CF complications including but not limited to hepatobiliary, gastrointestinal, and pulmonary conditions
- Pulmonary exacerbations and respiratory microbiology
- Serious safety outcomes

2. Pregnancy
   - Live birth
   - Stillbirth
   - Spontaneous abortion
   - Therapeutic abortion
   - Gestational age
   - Congenital anomalies
3. Drug utilisation
   - Ivacaftor exposure in patients with CF
4. CF disease progression
   - CF lung disease severity based on percent predicted FEV_1
   - Clinical signs of CF disease progression
   - Change in lung function over time

9.3.4 Statistical Analyses

Data analyses will be performed by the CF Trust and CF Foundation to meet the study objectives. The results of the annual analyses will be reported in the study report.

The primary objectives of this study are to evaluate long-term safety, pregnancy outcomes, drug utilisation, and CF disease progression in patients treated with ivacaftor. Descriptive statistics will be calculated for all endpoints. All safety, pregnancy, and CF disease progression endpoints will be compared between the Ivacaftor and Comparator Cohorts or between the Ivacaftor Pregnancy and Comparator Pregnancy Cohorts. Safety and pregnancy outcomes will also be described for the Historical Cohort. Annual incidence rates will be calculated for safety outcomes (Objective 1). Crude relative risks or risk difference with 95% confidence intervals will be calculated for some outcomes, as appropriate. Statistical modelling with adjustment for confounders and effect modifiers will be conducted, as possible, due to the likely sparse data. Identification of confounders and effect modifiers will be performed using stratified analyses. Each annual report will include the patient data from the previous calendar year (e.g., annual cross-sectional analysis). Longitudinal analyses will be included, as appropriate, in the final report.

This section presents a summary of the planned statistical analyses for this study (see Stand-alone Document 4 listed in Annex 1. List of Stand-alone Documents). A detailed

analysis plan will be presented in a statistical analysis plan. A summary of the comparisons to be made for each objective is provided in Table 5.

Table 5 Comparisons by Primary Objective

Objective	Setting	Cohorts Included	Comparisons
1. To evaluate the long-term safety of ivacaftor in patients with CF	UK, US	Ivacaftor; Comparator; Historical	• Comparison of long-term safety between the Ivacaftor Cohort (ivacaftor-treated patients) and the Comparator Cohort (concurrent nonexposed patients) to include relative risks or risk differences • Descriptive statistics for the Historical Cohort (historical nonexposed patients) will be available for comparison to the Ivacaftor Cohort (ivacaftor-treated patients). Comparisons to be based on 95% confidence intervals.
2. To evaluate the outcomes of pregnancy in ivacaftor-treated patients	UK, US	Ivacaftor Pregnancy Study; Comparator Pregnancy Study; Historical	• Comparison of pregnancy outcomes between the Ivacaftor Pregnancy Study Cohort (ivacaftor-treated patients) and the Comparator Pregnancy Study Cohort (concurrent nonexposed patients) • Descriptive statistics for the Historical Cohort (historical nonexposed patients) will be available for comparison to the Ivacaftor Pregnancy Study Cohort (ivacaftor-treated patients). Comparisons to be based on 95% confidence intervals.
3. To evaluate the drug utilisation of ivacaftor	UK, US	Drug Utilisation	All ivacaftor-treated patients will be included in the drug utilisation analysis. No comparisons will be made.
4. To evaluate CF disease progression in ivacaftor-treated patients	UK, US	Ivacaftor Comparator	• Comparison of CF disease progression between the Ivacaftor Cohort (ivacaftor-treated patients) and the Comparator Cohort (concurrent nonexposed patients)

CF: cystic fibrosis; UK: United Kingdom; US: United States.

9.3.4.1 Safety (Objective 1)

Safety outcomes for the Ivacaftor Cohort and the Comparator Cohort will include 6 main categories: death, organ transplantation, hospitalisations, CF complications, and pulmonary exacerbations and respiratory microbiology, and serious safety outcomes (composite outcome). The safety outcomes will be analysed for the Historical Cohort.

1. Death: Frequency of death will be calculated and will include cause of death and age at death. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.
2. Organ transplantations: Frequency of organ transplantations will be calculated and will include type of organ transplanted and age at transplant. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.

3. Hospitalisations: Frequency of hospitalisations will be calculated and will include the number of days of hospitalisation, and age at hospitalisation. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.
4. CF complications: Frequency of CF complications will be calculated. CF complications include infections, arthritis, asthma, bone fracture, diabetes, and several hepatic, gastrointestinal, and pulmonary complications. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.
5. Pulmonary exacerbations and respiratory microbiology: Frequencies of pulmonary exacerbations and respiratory microorganisms will be calculated. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.
6. Serious safety outcomes: Frequency of serious safety outcomes will be calculated. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.

9.3.4.2 Pregnancy (Objective 2)

Frequency and outcomes of pregnancies will be analysed for patients exposed to ivacaftor in the Ivacaftor Pregnancy Cohort and for patients in the Comparator Pregnancy Cohort. Pregnancy outcomes include live birth, stillbirth, spontaneous abortion, therapeutic abortion, undelivered, and unknown. Pregnancy outcomes of gestational age and congenital anomalies of the infant will be described for the CF Trust Patient Registry data. Pregnancies will be described by outcome, age, and duration of ivacaftor exposure. Pregnancy outcomes will also be described for the Historical Cohort.

9.3.4.3 Drug Utilisation (Objective 3)

Drug utilisation of ivacaftor will be described by analysing the Drug Utilisation Cohort. Frequency of ivacaftor exposure by *CFTR* genotype class, age, sex, and percent predicted FEV_1 will be calculated.

A separate description of drug utilisation analyses for other EU patient registries is provided in Annex 3: Additional Information.

9.3.4.4 CF Disease Progression (Objective 4)

In addition to the analyses of death and organ transplant described in Section 9.3.4.1, CF disease progression will be described by analysing the outcomes of CF disease severity and clinical signs of CF disease progression. These outcomes were chosen because they provide the most clinically meaningful description of CF disease progression given the data available in the registries.

CF disease progression will be assessed by comparing changes in health status amongst patients in the Ivacaftor Cohort to those in the Comparator Cohort on relevant disease progression variables. Disease progression variables include CFRD, DIOS, lung disease, and weight and will be assessed annually. Change in disease progression will be assessed when

there are sufficient data available (e.g., change from 2013 health status to 2014 health status will be analysed during 2015).

Health status for CFRD and DIOS will be dichotomous (yes/no or present/absent).

Health status for lung disease severity will be derived from the best annual assessment of percent predicted FEV_1, as

- Mild/Normal if percent predicted FEV_1 ≥70%,
- Moderate if percent predicted FEV_1 is ≥40% to <70%,
- Severe if percent predicted FEV_1 is <40%.[2]

Percent predicted FEV_1 will be calculated based on the equations of Hankinson et al.[30] or Wang et al.[31] The Hankinson standard will be used for male patients 18 years and older and female patients 16 years and older. The Wang standard will be used for male patients aged 6 to 17 years and for female patients aged 6 to 15 years.

Health status for weight will be based on the relative change from baseline in weight, which will be categorised into meaningful groupings based on the observed results (e.g., -10% to -5%, -5% to 0, 0 to 5%, 5% to 10%). Additionally, for children, percentiles of weight, adjusted for age and height, will be categorised into meaningful groupings. Weight will be explored and included if possible.

In general, the frequency and percentage of patients having each clinical sign (or state if a clinical sign has multiple states possible) will be reported. Shifts in state over time will also be reported. Analyses will be stratified by duration of ivacaftor exposure, age, sex, *CFTR* genotype class, percent predicted FEV_1, and comorbid conditions.

The primary analysis will include only those patients with necessary data points available. The effect of missing data will be assessed with sensitivity analyses, as appropriate.

Analysis of change in lung function over time will be based on percent predicted FEV_1. Descriptive statistics will be presented for the mean at each year and the mean change from Year 1 to the subsequent years. These analyses will include Ivacaftor Cohort patients with evidence of ivacaftor exposure and pulmonary function test results in each of the years in the analysis (e.g., evidence of ivacaftor exposure and FEV_1 results in 2012, 2013, and 2014 for the analysis of change in lung function from 2012 to 2014). Similarly, patients in the Comparator Cohort will include patients with no evidence of ivacaftor exposure in each of the years in the analysis.

9.3.5 Confounders and Effect Modifiers

Other variables, such as duration of prior ivacaftor exposure, pulmonary function, pulmonary microbiology (e.g., *P aeruginosa*), concomitant medications (e.g., dornase alfa, azithromycin), pancreatic sufficiency status, diabetes status, or health care utilisation, will be assessed as confounders and effect modifiers in the statistical analyses through stratification and adjustment, when possible.

9.4 Data Sources

More than 97 paediatric and 35 adult CF care centres in England, Scotland, Wales, and Northern Ireland enter data into the CF Trust Patient Registry database for all patients who consent to participate. More than 110 CF Foundation-accredited care centres in the United States enter data into the CF Foundation Patient Registry for all patients who consent to participate.

All data for the CF Trust and CF Foundation is entered into PortCF, the online registry application, by staff at CF-accredited care centres. Data are entered throughout the year for encounter-based and annual patient visits, whilst summaries of data collected are produced annually (i.e., registry annual reports). Analyses for this PASS will be conducted annually and provided as the yearly reports.

Questionnaires of the CF Trust and CF Foundation patient registries are provided as Stand-alone Documents 1 and 2, respectively (listed in Annex 1. List of Stand-alone Documents). The demographics form captures basic information about the patient, including death date when applicable. The diagnosis form indicates diagnosis and reason for diagnosis and captures genotype testing results. The encounter form is intended to capture data from a clinic visit and includes medications, complications, pulmonary function tests, respiratory microbiology results, laboratory tests, and height and weight. The episode form captures dates and reasons of hospitalisations. The annual review form is a yearly assessment of treatment, transplant status, pregnancy, and socioeconomic data.

For the drug utilisation objective, additional EU-based data sources are under investigation.

9.5 Study Size

The number of patients included in annual analyses will be dependent on the use of ivacaftor amongst patients in the registries. Ivacaftor is indicated for the treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene. The estimated prevalence of the *G551D* mutation is approximately 2374 patients globally. Based on 2010 data, the CF Trust has enrolled 432 patients with the *G551D* mutation and the CF Foundation has enrolled 1035 patients with the *G551D* mutation.[1,2] By working with these patient registries, we expect to be able to analyse more than half of the *G551D* patients in the world. Assuming that most *G551D* patients are indicated for treatment with ivacaftor and will receive treatment, the number of patients analysed is expected to be sufficient to achieve the objectives of the study.

The power to detect a difference in death rates between the Ivacaftor Cohort and the Comparator Cohort are presented in the table below. The death rate in the unexposed group, 103 of 9385 (0.011), was obtained from the 2010 UK Trust Annual Report and is shown below as Proportion 1. Proportion 2, the death rate in the Ivacaftor Cohort, is varied between 138 in 10,000 (0.0138) to 440 in 10,000 (0.0440).

Table 6 Power Calculations for Detecting Differences in Death Rates

Relative Risk	Proportion 1	Proportion 2	Alpha	Power (N Exposed = 432[a])	Power (N Exposed = 1035[b])
1.25	0.011	0.0138	0.1	0.111	0.180
1.5	0.011	0.0165	0.1	0.190	0.347
1.75	0.011	0.0193	0.1	0.287	0.534
2	0.011	0.0220	0.1	0.393	0.703
2.25	0.011	0.0248	0.1	0.501	0.829
2.5	0.011	0.0275	0.1	0.604	0.911
2.75	0.011	0.0303	0.1	0.695	0.958
3	0.011	0.0330	0.1	0.772	0.981
3.25	0.011	0.0358	0.1	0.834	0.992
3.5	0.011	0.0385	0.1	0.882	0.997
3.75	0.011	0.0413	0.1	0.919	0.999
4	0.011	0.0440	0.1	0.945	1.000

Note: Power is from a single-sided Fisher exact test of 2 proportions, with alpha = 0.1, assuming equal N per group (Ivacaftor Cohort and Comparator Cohort). Because the number of patients exposed is based on the "best-case scenario" (i.e., all eligible patients receiving ivacaftor), the power is likely higher than actual.

[a] CF Trust

[b] CF Foundation

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 Cystic Fibrosis Trust Patient Registry

Within the CF Trust Patient Registry, there are inbuilt verification tools that will "flag-up" any abnormal values that are out of the normal ranges directly to the sites and, in some instances, to the Registry Team. Throughout the year, regular (monthly) data verification is carried out by the Registry Team, running programmes looking at unusual data entries (e.g., abnormal height and weight). Any queries are then reported back to the sites for verification. Any duplicate registration of patients is also checked on a monthly basis, and if found, records are merged with no loss of data, thus maintaining a "clean" data set of patients.

Following the annual data cut, extensive data cleaning is undertaken in conjunction with the Bio-Statisticians at Imperial College London.

Data completeness is assessed each year. For patients known to be alive, 89% have evidence of at least an annual encounter in the CF Trust Patient Registry database. For patients with at least an annual encounter visit, 95% have evidence of pulmonary function measure (e.g., FEV_1).

9.6.2 Data Management for Cystic Fibrosis Foundation Patient Registry

CF Foundation imports data from the registry back-end 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 CF Foundation attempts to do as little corrections to the raw data as possible. Only authorised CF Foundation employees have access to the database. Details of the data management processes at the CF Foundation are provided in Stand-alone Document 3 (listed in Annex 1. List of Stand-alone Documents).

Data completeness in the CF Foundation Patient Registry is stimulated by tying up the amount of annual grant awards to the CF centres to the quality of data entered to the registry. As a result, 94% of patients' records in 2011 had medications data, 91% had complications data, and 91% had microbiology data. In addition, 96% of CF nontransplant patients 6 years or older and known to be alive had recorded pulmonary function test measurements.

9.7 Data Analysis

Some data analysis methods are provided in Section 9.3. A detailed analysis plan will be presented in a statistical analysis plan.

9.8 Quality Control

9.8.1 Quality Control for Cystic Fibrosis Trust Patient Registry

The UK CF Trust 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 Amsterdam 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 seen by the user site, and data cannot be moved between sites without the Registry Team being involved. The registry is in the process of receiving the Short Leap Shared Protection Certificate and has the Secure Site Pro Secure Sockets Layer Certificate required for large databases.

The registry is operated by the CF Trust in a password-protected, locked office in accordance with the ethical requirements for approval of the registry. 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. Visit logs will be kept up to date. Random sets of patients' notes are also checked at the visits to ensure no bias in the registry data.

During this study, the 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 also available by e-mail and telephone.

9.8.2 Quality Control for Cystic Fibrosis Foundation Patient Registry

The responsibility for the quality of the CF Foundation 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. Understanding an importance of additional assurances in the quality of the registry data, CF Foundation will be conducting an audit of 5% of the registry records annually.

9.9 Limitations of the Research Methods

Limitations of missing data

Missing data may introduce misclassification of exposure and outcomes in observational studies. The CF Trust and CF Foundation patient registries have robust systems in place to minimise missing data in their patient registry databases. These procedures are described in the data management and quality control sections (Sections 9.6 and 9.8). For the CF Trust, data completeness is assessed each year. Of patients known to be alive, 89% have evidence of at least an annual encounter in the CF Trust Patient Registry database. Amongst patients with at least an annual encounter visit, 95% have evidence of pulmonary function measure (e.g., FEV_1). For the CF Foundation, data completeness in the CF Foundation Patient Registry is stimulated by associating the amount of annual grant awards to the CF centres to the quality of data entered. As a result, 94% of patients' records in 2011 had medications data, 91% had complications data, and 91% had microbiology data. Additionally, 96% of CF nontransplant patients 6 years or older and known to be alive had recorded pulmonary function test measurements. Whilst missing data are minimised in the patient registries, exploratory and sensitivity analyses will be employed to understand the impact of missing data on the primary objectives of the study.

Limitations of observational studies

The nature of observational studies with nonrandom treatment assignment allows for the concern of selection bias. The concern is that patients treated with ivacaftor could be systematically different and have different risk factors for adverse events than patients who choose other treatments or are not eligible for ivacaftor. The design strategy of this study is a matched-comparator cohort (patients who have not been exposed to ivacaftor). Selection bias will be minimised by matching on age group, *CFTR* genotype class, and sex, as appropriate. Other variables that may influence selection bias, such as pancreatic sufficiency status or diabetes status, will be assessed as confounders in the statistical analyses through stratification and adjustment, when possible.

Another limitation of the observational study design is differential follow-up of the patient cohorts, which can introduce ascertainment bias of outcomes. To minimise this bias, the CF patient registries collect comprehensive data at least annually on all patients enrolled. To identify whether ascertainment bias is introduced into the study, cohorts will be compared for healthcare utilisation including CF care visits and hospitalisations.

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 study setting

The analysis of CF disease progression will be limited to CF lung disease severity and clinical signs of CF disease progression, based on definitions accepted in the medical community. Although the change in lung function over time will be analysed, the analysis is limited by differences in the frequency of data collection for pulmonary function testing. Pulmonary function test results are collected in both the CF Trust and the CF Foundation patient registries. However, the CF Trust database collects pulmonary function test results at the annual encounter only, whilst the CF Foundation allows CF care providers to enter pulmonary function test results for all patient encounters throughout the year. In either case, data are collected only if available. Additionally, the CF Trust collects only the best pulmonary function test result (newly implemented in 2012), whereas the CF Foundation collects the actual result at each encounter.

Whilst the patient registries do not provide the precision of a clinical study where all patients have pulmonary function testing at a defined and frequent interval, the available pulmonary function test data will be used to define CF lung disease severity (see Section 9.3) and provides a qualitatively accurate measurement of CF disease progression amenable to annual reporting. Given the variability in the number of data points available for each patient, analysis of the change in lung function over time utilising registry data is likely underpowered to detect differences between the Ivacaftor and Comparator Cohorts.

Limitations of the use of a Historical Cohort

The use of a Historical Cohort may also introduce bias in several ways. Data from a Historical Cohort are, by definition, different from the Comparator Cohort (selected from the same period as the Ivacaftor Cohort) because the CF care (e.g., medications, nonpharmacologic therapies, and treatment guidelines) have changed over time. Additionally, because the majority of patients with the *G551D* mutation are likely to be currently receiving ivacaftor, the Historical Cohort is likely to comprise the same patients, but at a different disease state (e.g., higher lung function, fewer clinical signs, and symptoms). The data fields for the registries are also modified slightly over time, limiting the ability to directly compare data from the Historical Cohort with those of cohorts based on more recent time periods.

Limitations on power and sample size

The number of patients included in annual analyses will be dependent on the use of ivacaftor amongst patients in the registries. As of 2010, the enrollment of patients with the *G551D-CFTR* mutation is 432 in the CF Trust and 1035 in the CF Foundation.[1,2] Therefore, the power to detect differences in the study endpoints is limited. Whilst we explored the study power for detecting differences in mortality, the study is powered to detect 2- to 3-fold differences between study cohorts. One method to increase power would be to combine data from individual patient registries. Combining data sources was previously considered by the leadership of the patient registries in the UK and US independent of this study protocol, and they advised that previous pooled analysis has been limited to matching at the encounter level and methods for combining annual data have not been established. Throughout the conduct of the study, the feasibility of combining annual registry data will be further explored.

Limitations on the analyses for prior hypotheses

Given the scientific interest in the assessments of pulmonary exacerbations and adverse events in the CF population, a null hypothesis would be that there is no difference in the incidence of these events between Ivacaftor and Comparator Cohorts or perhaps a lower incidence in the Ivacaftor Cohort. However, the analyses are limited by a number of factors. The lack of knowledge on the background risk of specific adverse events in the target CF population means that it is not possible to predict whether the number of patients in each registry will be sufficient to power the detection of statistically significant differences between the Ivacaftor and Comparator Cohorts. The small sample size may also lead to spurious results that may confound interpretation, and the manner in which pulmonary exacerbations are collected do not allow direct comparison to the incidence of pulmonary exacerbation observed in Phase 3.

For the specific prior hypothesis on pulmonary exacerbation, the CF Trust and CF Foundation 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. Further, because the data sets are based on existing registry variables, adverse drug reactions, and adverse events in the SmPC will rely on mapping variables and/or rely on CF care centres providing text entries that are mappable.

9.10 Other Aspects

The study duration is expected to be 5 years. At any time, Vertex may terminate this study in its entirety.

Conditions that may warrant termination include, but are not limited to:

- data are no longer available from CF Trust and/or CF Foundation,
- study objectives have been met, or
- decision by regulatory authority.

10 PROTECTION OF HUMAN SUBJECTS

The CF Trust and CF Foundation patient registries are conducted 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 CF Trust 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 Trust Patient 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 CF Foundation 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 will be obtained and maintained by the CF Trust and CF Foundation patient registries. Vertex will not have access to subject information. Informed consent is obtained by the CF Trust and CF Foundation as part of their registry enrolment procedures.

10.1.1 Informed Consent for the Cystic Fibrosis Trust Patient Registry

In the United Kingdom, the CF Trust Patient Registry consent procedures have been agreed upon with the National Research Ethics Service. In a recent review, procedures in the current PASS were approved and determined to be covered by the existing patient consent for participation in the CF Trust Patient Registry.

For the CF Trust Patient Registry, 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.

10.1.2 Informed Consent for the Cystic Fibrosis Foundation Patient Registry

The institutional review board (IRB) reviews all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. Data for the CF Foundation registry are only collected at sites where IRB approval has been obtained and for subjects for whom consent or assent (as applicable) is obtained. The registry protocol, sample ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents are provided to the IRB by the CF Foundation, as allowable by local applicable laws and regulations. The IRB must approve the ICF and assent (as applicable), which must meet national and local regulations.

Patients and their parent or legal guardian must also be informed that participation is voluntary and that they may withdraw from the registry at any time, without prejudice to their current or future care. Once all of their questions have been answered and the patients 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 ICF and assent (as applicable).

Informed consent and assent (as applicable) must be obtained from each patient and 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.

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 by the CF Trust and CF Foundation to Vertex using deidentified data.

All the information in the CF Trust 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 CF Trust 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 CF Foundation 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 following text is provided to patients enrolled in the CF Foundation Patient Registry:

> *"Registry data may be published, or presented at scientific meetings, but your/your child's identity will not be disclosed. However, representatives from the Food and Drug Administration, other national regulatory authorities, CF Foundation, and the [Institution IRB name] IRB monitors/representatives may inspect the research and clinical records without removal of identifying information.*
> *The CF Patient Registry is a permanent registry of health information and your authorisation for disclosure of your/your child's health information to the registry will be effective as long as the Patient Registry information is collected."*

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse reactions will not be reported on an expedited basis for this study because it is an observational cohort study designed to collect long-term safety information using secondary data. Safety listings will be received by Vertex annually from the patient registries. Individual case safety reports will be created as applicable to prevent duplicate reports in the global safety database. This is in line with EU Good Pharmacovigilance Practices VI.C.1.2.1, which specifies that, for noninterventional study designs that are based on secondary use of

data, adverse reactions reporting is not required. Reports of adverse events/reactions should only be summarised in the study report, where applicable.

All safety information will be assessed and submitted in analysis reports, which will be submitted according to the schedule agreed as part of the post-authorisation commitment for this study. A full review of the safety information collected for the full study period will be presented in the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Synopses of interim study reports and final study report will be annexed to the RMP (Annex 9). Study results will be used to adjust the safety specification (Part II-SV) and the pharmacovigilance plan (Part III) of the Risk Management Plan. In addition, interim and final study results will be periodically and critically discussed in Periodic Safety Update Report Sections 7 and 8, EU Regional Appendix "Reporting of Results From Post-Authorisation Safety Studies," and also summarised in the Development Safety Update Report Section 9.

Vertex plans to publish the study results after the final study analysis is completed in collaboration with the CF Trust and CF Foundation. Vertex recognises that the CF Trust has a responsibility under the Research Governance Framework for Health and Social Care to ensure that results of scientific interest arising from this study are appropriately published and disseminated. CF Trust employees and the principal investigator shall be permitted to present at symposia, national, or regional professional meetings and to publish in journals, theses, or dissertations, or otherwise of their own choosing, the methods and results of the study. Any publication by the CF Trust or CF Foundation shall not be made before the first study publication, which shall be made by Vertex 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). Publications proposed by the CF Trust will be reviewed by Vertex before submission for publication or presentation. The CF Trust shall consider in good faith all comments received from Vertex during the review period.

13 REFERENCES

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14 ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference	Date	Title
1.	CF Trust - Questionnaires	2011	2011 CF Trust Patient Registry Questionnaires
2.	CF Foundation - Questionnaires	2011	2011 CF Foundation Patient Registry Questionnaires
3.	CF Foundation - Data Management	2012	CF Foundation Patient Registry Data Management Procedures
4.	Vertex Form WI-0026c (Version 2.0)	2012	Pregnancy Safety Information Collection Form
5.	Study statistical analysis plan	2013	Statistical Analysis Plan Methods Interim Analysis 1 for Ivacaftor Long-term Safety Study (Draft 0.1)

CF: cystic fibrosis.

15 ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

16 ANNEX 3: ADDITIONAL INFORMATION

16.1 Analysis of Data From Other European Patient Registries

16.1.1 Rationale and Background

At the request of the Pharmacovigilance Risk Assessment Committee, other European patient registries were considered for inclusion in this study.

For Objectives 1, 2, and 4, the first step of feasibility assessment included consideration of sample size for comparative analyses with multiple stratification variables. Upon examination of the prevalence of the *G551D* mutation amongst European countries, the feasibility assessment was focused on France, Germany, and Ireland. Based on numbers from the European CF Society Patient Registry (ECFSPR), these 3 countries represent approximately 84% of the *G551D* or Kalydeco-eligible population and approximately 64% of the overall CF population in the 20 countries participating in the ECFSPR.[1] France, Germany, and Ireland each have at least 100 Kalydeco-eligible patients.

The next step of feasibility assessment includes determination of data collection content, frequency, quality, and availability to sponsors. For Objective 3, a similar approach was taken, with a focus on sample size and data availability.

Table 7 provides a summary of the registries evaluated. Detailed feasibility assessments are provided in Sections 16.1.2 to 16.1.2. Information for the CF Trust (UK) and CF Foundation (US) is provided as a reference.

Table 7 National Patient Registries Considered for Inclusion in the Study

Parameter	UK	US	Ireland	France	Germany	ECFS
Estimated national percentage of patients with CF in registry	>99%	90%	91%	90%	90%	14% to 100%[a]
Number of *G551D* patients in registry	432	1035	125[b]	62[c]	192	Unknown[c]
Data collection frequency	Encounter-based	Encounter-based	Annual	Annual	Annual for 100% patients; encounter-based for ~70%	Less than annually (2008-2009 data collected and analysed in 2012)
Include in analyses						
Safety (Objective 1)	Yes	Yes	No	No	No	No
Pregnancy (Objective 2)	Yes	Yes	No	No	No	No
Drug utilisation (Objective 3)	Yes	Yes	Yes	Yes	No	No

Table 7 National Patient Registries Considered for Inclusion in the Study

Parameter	UK	US	Ireland	France	Germany	ECFS
CF disease progression (Objective 4)	Yes	Yes	No	No	No	No

Sources: Kalydeco EU Risk Management Plan, CF Trust Patient Registry, [2] CF Foundation Patient Registry, [3] CF Registry of Ireland.[4] French CF Registry,[5] German CF Quality Assurance Project,[6] and ECFSPR.[1]

CF: cystic fibrosis; ECFSPR: European Cystic Fibrosis Society Patient Registry; UK: United Kingdom; US: United States.

[a] The 20 countries in the ECFSPR have varying national coverage from 14% to 100%.

[b] The number of patients in the CF Registry of Ireland only includes those with *G551D/F508del-CFTR* and *G551D/G551D-CFTR* genotypes.

[c] The number of patients in the French CF Registry only includes those with the *G551D/F508del-CFTR* genotype.

[c] The ECFSPR reports the number of alleles in their database. *G551D-CFTR* comprise 410 alleles out of 27753 alleles in the registry. The countries with the highest incidence of the *G551D-CFTR* allele are Ireland, Germany, and France.

16.1.2 European Cystic Fibrosis Society Patient Registry

The ECFSPR is a collection of patient data from 20 countries and comprises data collected by national registries and, for countries without national registries, by CF centres.[1] The ECSFPR represents varying percentage of the known CF population in the participating countries (e.g., 14% of the CF population in Italy to 100% in Denmark) and include approximately 18000 patients with CF.

16.1.2.1 Variables for European Cystic Fibrosis Society

Variables include

- demography (CF centre code, patient code, year of follow-up, date of birth, sex, status of patient [alive on 31 December of this year; died during this year], cause of death [respiratory, liver, trauma, suicide, transplantation, non-CF related], and date of death);
- genotype (first and second mutation);
- therapy (includes inhaled continuous hypertonic saline this year, inhaled continuous antibiotics this year, inhaled continuous bronchodilators this year, in oxygen therapy this year, use of rhDNase this year, use of continuous azithromycin [or other macrolide] this year, use of ursodeoxycholic acid this year, and use of pancreatic enzymes this year);
- diagnosis (includes diagnosis confirmed, age at diagnosis in year, type of sweat test, electrolytes, chloride value, meconium ileus, and neonatal screening);
- follow-up (date of best FEV_1 registered this year, value of best FEV_1 registered this year, value of best FVC registered this year, weight measured at date of best FEV_1 or, if no lung function test, last weight of the year of follow-up, and height measured at date of best FEV_1 or, if no lung function test, last height of the year of follow-up);

- complications (ABPA, diabetes [daily insulin treated this year], pneumothorax requiring chest drain this year, liver disease this year, hemoptysis major over 250 mL this year, pancreatic status [faecal elastase, faecal fat], and occurrence of malignancy this year);
- microbiology (includes chronic *B cepacia* complex, nontuberculous mycobacteria this year, chronic *P aeruginosa*, chronic *S aureus*, and *Stenotrophomonoas maltophilia* this year); and
- transplant (liver transplant, year of latest liver transplant, lung transplant, and year of latest lung transplant).

16.1.2.2 Data Management and Quality Control

The collection of data is fully computerised. Data are directly sent by the users in an encrypted form to the central database. This process included considerable effort from all parties involved: national registries, individual centres, and their national coordinators, the ECFSPR help desk, and the statistician team.

The data are collected through ECFRecord (software developed for the ECFSPR) and are sent to a central database either through the uploading and transmission of data files—where a national registry already exists—or through the manual data entry feature. The national registries contribute the majority of patient data in the ECFSPR, but individual centres and new countries are joining the registry. Individual centres contributed approximately 10% of the data in the ECFSPR in 2008/2009.[1]

16.1.2.3 Feasibility Assessment

Use of data from the ECFSPR is not currently feasible for the objectives of this study. The ECFSPR does not have patient consent to collect data directly for use by pharmaceutical companies. Thus, for example, patients receiving ivacaftor could be identified if the national registry and individual centres providing data to the ECFSPR collect the variable or if additional patient consents, data collection forms, and/or software modifications are implemented at the national registry/individual centre level to enable the ECFSPR to provide a consolidated data set to Vertex. Further, the technical challenges of compiling data from the 20 contributing countries mean that the ECFSPR database has a longer lag between the calendar year of data collection and that of data reports (e.g., 2008/2009 data reported in the annual report published in 2013). Given that Ireland, France, and Germany together comprise 60% to 65% of the number of patients in the ECFSPR and the majority of patients in the ECFSPR with the *G551D-CFTR* mutation,[1] the ECFSPR will not be used in the analyses of the objectives of this study.

16.1.3 Cystic Fibrosis Registry of Ireland

The CF Registry of Ireland (CFRI) represents 91% of the known CF population in the Republic of Ireland and includes 1073 patients with CF (approximately 3% of the CF population in the EU), of which 125 have *G551D/F508del* or *G551D/G551D* alleles on their *CFTR* gene.[4] The number of patients with CF is collected via the annual census. Upon consent, patient data are collected by the CFRI on an annual basis.

16.1.3.1 Variables for Cystic Fibrosis Registry of Ireland

Variables include[7]

- diagnosis details (diagnosis tests [e.g., sweat test results], genotype, symptoms/method of diagnosis, age at diagnosis) and
- annual assessment details (number of hospitalisations between annual assessments, complications, pulmonary function tests, chest X-ray reports, clinical chemistry, infections [cultures and treatments], long-term therapies, vaccinations/immunisations, physiotherapy summary, nutritional summary, transplant status, social details such as number of days off work or school in previous 12 months).

Starting in 2013, use of ivacaftor will be collected as a variable.

16.1.3.2 Data Management and Quality Control

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. The CFRI is registered under 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.

Annual assessment data were collected for 91.1% of paediatric patients and 69.4% of adult patients in 2011. Data on hospitalisations and pulmonary exacerbations can often be incomplete for adults.[4]

16.1.3.3 Feasibility Assessment

Patient data are collected manually by CFRI clinical research associates from patients' medical records at CF centres and clinics across Ireland. Whilst efforts are underway to train regionally-based staff to enter the required data, this will not be in place for a number of years. Current data collection and entry into the database and data cleaning are a 7-month process (i.e., patient data collected at the sites by the close of each calendar year are not available as a data set until July of the following year). Ongoing improvements to software systems are expected to shorten this timeline.

Because data recording practices differ across hospitals, data for hospitalisations and respiratory exacerbations may be incomplete for each patient in the CFRI. After communications with Mr. Godfrey Fletcher, the Chief Executive Officer of the CFRI, it was mutually agreed upon that, based on the upcoming upgrades to the patient registry and the limitations on the current annual data collection scheme, CFRI data are not suitable for analysis of the safety, pregnancy, and disease progression objectives of the study. However, the data could be used for the drug utilisation analysis for ivacaftor.

Therefore, data from the CFRI will be analysed only to address the drug utilisation for ivacaftor (Objective 3).

16.1.4 French Cystic Fibrosis Registry

The French CF Registry (Registre français de la mucoviscidose) represents >90% of the known CF population in France and include approximately 6500 patients with CF[8] (approximately 18% of the CF population in the EU), of which approximately 62 have the *F508del/G551D* alleles in the *CFTR* gene.[5]

The population comprises patients with CF followed in the care centres participating in the registry in France (metropolitan France, Reunion Island, and Guadeloupe). Data are collected once a year by means of a questionnaire transmitted using Web, paper questionnaires, or exports from electronic patient files. The information requested refers to the preceding year and includes semi-anonymous patient identification, diagnosis, medical follow-up, treatments used, anthropometric data, respiratory function, bacteriological data, evolution of the condition, and social and family situation. Statistical analysis is performed on anonymised data.[5]

16.1.4.1 Variables for the French Cystic Fibrosis Registry

Variables include

- demographics,
- mortality;
- pregnancy
- CF diagnosis (including genotype),,
- medical follow-up,
- treatments used,
- anthropometric data (including height and weight),
- spirometry (including FEV_1, FVC),
- microbiology (at least 1 sputum during the year with select microorganisms),
- complications (respiratory, gastrointestinal, diabetes, other),
- transplantations,
- hospitalisations and outpatient visits,
- therapeutic management (use of intravenous antibiotic courses, antibiotic courses, respiratory therapeutics, aerosoltherapy treatments, digestive and nutritional treatments); and
- social data (employment and marital status).

16.1.4.2 Data Management and Quality Control

Data are collected once a year by means of a questionnaire transmitted using Web, paper questionnaires, or exports from electronic patient files. The information requested refers to the preceding calendar year and includes semi-anonymous patient identification.

16.1.4.3 Feasibility Assessment

The French CF Registry has been collecting data on patients with CF since 1992, and a new objective to cover the entire population of patients with CF in France was added in 2006. In 2012, the registry began collecting information on ivacaftor use amongst its patients. Based on the frequency of data collection (annual) and the number of patients exposed to ivacaftor, the French CF registry is not suitable for analysis of safety, pregnancy, and disease progression. After communications with Lydie Lemonnier, manager of the French CF Registry, it was agreed that the data were available and suitable for the drug utilisation analysis.

16.1.5 German Cystic Fibrosis Quality Assurance Project

The German CF Quality Assurance Project (Qualitätssicherung Mukoviszidose) was started in 1995 as a basic CF registry and includes approximately 8700 patients with CF from outpatient clinics and health care centres.[6] In 2011, the *G551D* mutation accounts for approximately 1.4% of the known *CFTR* alleles in the registry.

The population comprises patients with CF followed in the care centres participating in the registry in Germany. Data are collected once a year through MUKO.dok, a new client-server application system fully implemented in 2012. The software is currently implemented at 93 centres; 41 centres report encounter-based data, whereas other centres report annually.

Patients consent to have their data in the registry for CF treatment quality assurance purposes, scientific research, and collection and assessment of safety profiles of registered drugs. The informed consent is approved by a dedicated Data Protection representative, and a central ethics committee approves data collection and study-specific procedures.

16.1.5.1 Variables for German Cystic Fibrosis Quality Assurance Project

Variables include

- core data (personal data and demographics);
- clinical core data, including CF diagnosis (reasons [neonatal screening, clinical signs, family history, other] and criteria [sweat text, genotyping, nasal potential difference, rectal short circuit current]) and initial colonisation (*P aeruginosa*, *S aureus*, methicillin-resistant *S aureus*/oxacillin-resistant *S aureus*, *Burkholderia*, *S maltophilia*, *Haemophilus influenzae*, *Alcaligenes xylosoxidans*);
- diagnoses (of medical conditions);
- medications;
- nonpharmacologic treatments;
- social and family situation; and
- history data, comprising social, clinic, lung function, microbiology, laboratory, sonography, CF complications (respiratory symptoms, pulmonary exacerbations, hospitalisations, pulmonary function testing, microbiology, laboratory results [clinical parameters, sonography, X-ray]), nutritional status, other procedures).

16.1.5.2 Data Management and Quality Control

Data are collected in 2 steps. In Step I, lung function, nutrition, microbiology data, and therapy groups are evaluated for all patients. In Step II, a smaller group of patients undergoes more complete evaluation with regards to therapy details. The annual return in 2011 was 72% (reduced due to the introduction of the new software system MUKO.dok). Guidance and interpretation of variables are provided in the MUKO.dok user manual and through online, email, and telephone assistance.

A patient number is generated automatically by the system based on the mother's birthdate and the care centre number. The transfer and storage of patient data in the registry are pseudomised. Plausibility checks, checks for completeness, and checks for duplicate patient registration are preprogrammed in the software.

CF centres are not regularly monitored by the German CF Quality Management team. A data manager verifies and cleans the data by looking for unusual data entries. Statistical analyses are performed by the University in Hannover or University in Dresden.

16.1.5.3 Feasibility Assessment

Based on communication with Marguerite Höner, MSc (Clinical Project Manager, Qualitätssicherung Mukoviszidose) and Prof. Dr. Bukhard Tümmler (Pediatric Pulmonology, Medizinische Hochschule Hannover), due to issues of data quality and ongoing verification process, the German registry is not able to analyse their data for purposes outside of the registry. Data quality initiatives are ongoing to improve the registry data with the possibility of future analysis for drug utilisation purposes.

16.2 Drug Utilisation Subprotocol

The drug utilisation subprotocol will be conducted using the same Drug Utilisation Cohort definition (Section 9.1.2.6), analysis variables (Section 9.3.2.3), and statistical analysis (Section 9.3.4.3), as specified in the main protocol for Objective 3 (drug utilisation).

To meet the subprotocol objective, data for outcomes will be analysed separately for each registry starting at Year 2 of the main protocol. All enrolled patients exposed to ivacaftor will be included in the Drug Utilisation Cohort. Ivacaftor exposure will be derived as described for the CF Trust (Section 9.3.1.1) if start and stop dates of ivacaftor treatment are available, or as described for the CF Foundation (Section 9.3.2.1) if start and stop dates of ivacaftor treatment are not available.

Drug utilisation of ivacaftor will be described by the frequency of ivacaftor exposure, by *CFTR* genotype class, age, sex, and percent predicted FEV_1. Because ivacaftor was not available in Ireland and France until 2013, data for drug utilisation analyses will not be available for Vertex until 2014; therefore, data will be analysed separately for each registry for 4 years. The milestones for the annual reports are provided in Table 8.

Table 8 Subprotocol Study Milestones

	Planned Dates	
Milestone[a]	**Ireland**	**France**
Start of data collection[b]	May2014[c]	May 2014[c]
End of data collection[b]	May 2017	May 2017
Year 1 Report	not applicable	not applicable
Year 2 Report	October 2014	October 2014
Year 3 Report	October 2015	October 2015
Year 4 Report	October 2016	October 2016
Registration in EU PAS Register[d]	tbd	tbd
Final report of study results	October 2017	October 2017

CF: cystic fibrosis; EU PAS: European Union Post-authorisation Study; tbd: to be determined.

[a] Milestones are based on the main protocol (i.e., the Year 1 Report is relative to the start of data collection for the CF Trust [UK] and CF Foundation [US] registries).

[b] 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.

[c] Because ivacaftor was not commercially available until 2013, data for drug utilisation analyses will not be available for extraction until 2014. Therefore, subprotocol reports will begin with the Year 2 (relative to the main protocol).

[d] Study will be registered in EU PAS Register following Pharmacovigilance Risk Assessment Committee approval of final protocol and before study initiation.

16.3 References for Subprotocol

1 European Cystic Foundation Patient Registry. ECFS Patient Registry Annual Data Report: 2008-2009 data (Version 03.2012).

2 Cystic Fibrosis Trust. United Kingdom Cystic Fibrosis Registry: annual data report 2010. London, UK: Cystic Fibrosis Trust; 2012.

3 Cystic Fibrosis Foundation Patient Registry. 2010 Annual data report to the center directors. Bethesda, MD: Cystic Fibrosis Foundation; 2011.

4 Cystic Fibrosis Registry of Ireland. Annual Report 2011. Dublin, Ireland: Cystic Fibrosis Registry of Ireland; 2012.

5 Vaincre la Mucoviscidose and Institut National d'Études Démographiques. French CF Registry – Annual Data Report 2011. Paris: Vaincre la Mucoviscidose and INED; 2013.

6 Mukoviszidose e.V. und Mukoviszidose Institut gemeinnützige Gesellschaft für Forschung und Therapieentwicklung mbH. Berichtsband Qualitätssicherung Mukoviszidose 2011. Bonn, Germany: Mukoviszidose e.V. und Mukoviszidose Institut gemeinnützige Gesellschaft für Forschung und Therapieentwicklung mbH; 2012.

7 Cystic Fibrosis Registry of Ireland [Internet]. Types of information. Available at: http://www.cfri.ie/infotypes.php. Assessed 24 April 2013.

8 Association de Lutte Contre la Mucoviscidose – Vaincre la Mucoviscidose (Association Against Cystic Fibrosis – Beating Cystic Fibrosis)[Internet]. Les patients attents de mucoviscidose en France [updated 19 February 2013]. Available at: http://www.vaincrelamuco.org/ewb_pages/e/etre-muco.php. Accessed 25 March 2013.