Module 1.8.2

EU RISK MANAGEMENT PLAN (EU- RMP)

For KALYDECO (ivacaftor)

RMP Version Number: 16.0
Data lock for this RMP: 14 February 2024
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Rationale for submitting an updated RMP: This RMP was updated to reflect the completion of Study 126 (open-label study to evaluate the safety and pharmacodynamics of IVA in subjects with CF 1 to <24 months of age) and the completion of Study 125 (post-authorization efficacy study).

Summary of significant changes in this RMP:

- reflect the completion of Study 126 and Study 125;
- include the updated post-market pregnancy safety information collection form in Annex 4;
- The IVA exposure sections were also updated.

Other RMP versions under evaluation

RMP version number	Submitted on	Submitted within
N/A	N/A	N/A

Current approved RMP

RMP version number	Date of opinion	Approved with procedure
15.5	22 February 2024 (positive CHMP opinion)	EMEA/H/C/002494/IB/0123

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACFDR	Australian Cystic Fibrosis Data Registry
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration versus time curve
CF	cystic fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry (US)
CFLD	cystic fibrosis liver disease
CFRD	cystic fibrosis-related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DIBD	Developmental International Birth Date
ECFSPR	European Cystic Fibrosis Society Patient Registry
ECG	electrocardiogram
EEA	European Economic Area
EFD	embryo-foetal development
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
F508del	an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein
FEV_1	forced expiratory volume in 1 second
G551D	a missense mutation that results in the replacement of a glycine residue at position 551 of the CFTR protein with an aspartic acid residue
GD	gestation day
GLP	Good Laboratory Practices
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HLT	high level term
INR	international normalised ratio
IV	intravenous
IVA	ivacaftor
K_i	inhibition constant
LFT	liver function test
LOCS III	Lens Opacity Classification System, Version III
LTSS	Long-term Safety Study
LUM	lumacaftor
[redacted]	
MA	market authorisation
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
MRHD	maximum recommended human dose
MTD	maximum tolerated dose
N	number of subjects

Abbreviation	Definition
NA	not applicable
PAES	Post-authorisation Efficacy Study
PASS	Post-authorisation Safety Study
PD	person-days
PD	pharmacodynamic, pharmacodynamics
P-gp	permeability glycoprotein
PI	pancreatic insufficiency
PL	Patient Information Leaflet
PK	pharmacokinetic, pharmacokinetics
PND	postnatal day
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
PY	person-years
q12h	every 12 hours
QPPV	Qualified Person for Pharmacovigilance
QT	QT interval represents the duration of ventricular depolarisation and subsequent repolarisation
QTcF	QT interval corrected for heart rate with Fridericia's correction [$QTcF = QT/RR^{0.33}$]
R117H	*CFTR* missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
RMP	risk management plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOC	system organ class
SVPC	supraventricular premature complex
TEZ	tezacaftor
TK	toxicokinetic
TNF	tumor necrosis factor
UK	United Kingdom
ULN	upper limit of normal
US	United States
VX–770	ivacaftor

PART I Product(s) Overview

Active substance(s)	**KALYDECO**
Pharmacotherapeutic group(s) (ATC Code)	Other respiratory system products (R07AX02)
Market Authorisation Holder	Vertex Pharmaceuticals (Ireland) Limited
Medicinal products to which this RMP refers	Ivacaftor
Invented name(s) in the European Economic Area (EEA)	KALYDECO
Market authorisation procedure	Centralised
Brief description of the product	Ivacaftor is *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide.
	Ivacaftor is a selective potentiator of the CFTR protein, i.e., in vitro ivacaftor increases CFTR channel gating to enhance chloride transport. However, the exact mechanism leading ivacaftor to prolong the gating activity of some mutant CFTR forms has not been completely elucidated.
Hyperlink to the Product Information	(Current) Summary of Product Characteristics for KALYDECO
Indication(s) in the EEA	**Current (if applicable):** Kalydeco tablets are indicated • as monotherapy for the treatment of adults, adolescents, and children aged 6 years and older and weighing ≥25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.* • in a combination regimen with tezacaftor/ivacaftor tablets for the treatment of adults and adolescents aged 6 years and older with cystic fibrosis (CF) who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.* • in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene. Kalydeco granules are indicated • as monotherapy for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.* • in a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one *F508del* mutation in the *CFTR* gene
	Proposed (if applicable): • Not applicable

Dosage in the EEA	**Current (if applicable):** Kalydeco monotherapy • Adults, adolescents, and children aged 6 years and older and weighing ≥25 kg: one Kalydeco 150 mg film-coated tablet taken in the morning and one Kalydeco 150 mg tablet taken in the evening, approximately 12 hours apart with fat-containing food (300 mg total daily dose). • Children aged 6 months and older o One sachet of 25 mg granules taken in the morning and one sachet of 25 mg granules taken in evening, approximately 12 hours apart with fat-containing food, for children ≥5 kg to less than 7 kg in weight (50 mg total daily dose) o One sachet of 50 mg granules taken in the morning and one sachet of 50 mg granules taken in evening, approximately 12 hours apart with fat-containing food, for children ≥7 kg to less than 14 kg in weight (100 mg total daily dose) o One sachet of 75 mg granules taken in the morning and one sachet of 75 mg granules taken in evening, approximately 12 hours apart with fat-containing food, for children ≥14 kg to less than 25 kg (150 mg total daily dose) • Children aged 4 to <6 months o One sachet of 25 mg granules taken in the morning and one sachet of 25 mg granules taken in evening, approximately 12 hours apart with fat-containing food, for children ≥5 kg in weight (50 mg total daily dose) • Children aged 2 to <4 months o One sachet of 13.4 mg granules taken in the morning and one sachet of 13.4 mg granules taken in evening, approximately 12 hours apart with fat-containing food, for children ≥3 kg in weight (26.8 mg total daily dose) • Children aged 1 to <2 months o One sachet of 13.4 mg granules taken orally qd with fat-containing food for children ≥3 kg in weight Kalydeco in a combination regimen with tezacaftor/ivacaftor • Adults and adolescents aged 12 years and older and children aged 6 to less than 12 years weighing ≥30 kg: one tezacaftor 100 mg/ivacaftor 150 mg tablet taken in the morning and one Kalydeco 150 mg tablet taken in the evening, approximately 12 hours apart with fat-containing food. • Children aged 6 to less than 12 years weighing <30 kg: one tezacaftor 50 mg/ivacaftor 75 mg tablet taken in the morning and one Kalydeco 75 mg tablet taken in the evening, approximately 12 hours apart with fat-containing food. Kalydeco in a combination regimen with ivacaftor/tezacaftor/elexacaftor • Adults and adolescents aged 12 years and older and children aged 6 years to less than 12 years weighing ≥30 kg: two tablets (each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg) taken in the morning and one Kalydeco 150 mg tablet taken in the evening, approximately 12 hours apart with fat-containing food. • Children aged 6 to less than 12 years weighing <30 kg: two tablets (each containing ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 500 mg) taken in the morning and one Kalydeco 75 mg tablet taken in the evening, approximately 12 hours apart with fat-containing food. • Children aged 2 to less than 6 years weighing ≥10 to <14 kg: one sachet (each containing ivacaftor 60 mg/tezacaftor 40 mg/elexacaftor 80 mg) taken in the morning and one Kalydeco 59.5 mg sachet taken in the evening, approximately 12 hours apart. • Children aged 2 to less than 6 years weighing ≥14 kg: one sachet (each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg) taken in the morning and one Kalydeco 75 mg sachet taken in the evening, approximately 12 hours apart **Proposed (if applicable):** • Not applicable

Pharmaceutical form(s) and strengths	**Current (if applicable):** • 150 mg film-coated tablet • 75 mg film-coated tablet • 75 mg granules in sachet • 59.5 mg granules in sachet • 50 mg granules in sachet • 25 mg granules in sachet • 13.4 mg granules in sachet **Proposed (if applicable):** • Not applicable
Is/will the product be subject to additional monitoring in the EU	No

PART II Safety Specification

SI Epidemiology of Indication(s) and Target Population(s)

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. The target population for ivacaftor (IVA) monotherapy is patients with CF who have the *R117H-CFTR* mutation or one of the following gating (Class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*.

SI.1 Incidence

Europe: The incidence of CF in the European countries varies markedly, from 1 in 1,353 in Ireland to 1 in 25,000 in Finland.[1] Incidence for some European countries are: Austria 1 in 3500, Belgium 1 in 2850, Bulgaria 1 in 2500, Cyprus 1 in 7914, Czech Republic 1 in 2833, Denmark 1 in 4700, Finland 1 in 25,000, France 1 in 4700, Germany 1 in 3300, Hungary 1 in 4000, Italy 1 in 4238, Netherlands 1 in 4750, Norway 1 in 8642, Slovakia 1 in 1800, Slovenia 1 in 3000, Spain 1 in 3750, Sweden 1 in 5600, Turkey 1 in 3000, and UK 1 in 2381.[1,2]

US: In the US, among white persons, CF occurs in approximately 1 in 3,000 to 4,000 live births. In other races and ethnicities, CF occurs less commonly, including approximately 1 in 4,000 to 10,000 Latin Americans, 1 in 15,000 to 20,000 African Americans, and even less commonly in Asian Americans.[3] Approximately 850 new cases of CF are diagnosed each year in the US.[4]

Canada: Approximately 1 in 3600 children in Canada is born with CF. In 2017, 115 patients (mostly children) were diagnosed with CF.[5]

Australia: Approximately 1 in 3050 children in Australia was born with CF annually, from 1989 to 2006.[6] In 2017, 72 patients (mostly newborns) were diagnosed with CF.[7]

In 2017/2018, the number of patients 5 years of age or younger with CF were approximately 4200 (14%) in the US[4], 520 (13%) in Canada[5], 417 (13%) in Australia[7], and 145 (13%) in Ireland[8] In 2018, 1,093 (11%) patients in the UK were 7 years of age or younger.[9]

SI.2 Prevalence

General CF population

Over 30,000 people in the US and more than 70,000 people worldwide have CF.[4]

Europe: A survey of standards of care in Europe, EuroCareCF (2007 to 2009), estimated that there were 39,897 people with CF who were treated in 32 European countries.[2] According to another survey performed by Orphanet, the prevalence of CF in the EU is 7.4 per 100,000.[10]

The overall prevalence of CF across 27 countries in the EU in 2004 was estimated at 0.737 per 10,000, ranging from 0.10 in Latvia to 2.98 in Ireland.[1]

US: There were 30,775 patients in the US CF Foundation Patient Registry (CFFPR) in 2018, with an overall prevalence of 0.9 per 10,000 people.[4,11]

Canada: There were 4,309 patients in the Canadian CF Registry in 2017, with an overall prevalence of 1.2 per 10,000 people.[5,12]

Australia: There were 3,151 patients in the Australian CF Data Registry (ACFDR) in 2017, with an overall prevalence of 1.3 per 10,000 people.[7,13]

Target population

Of the more than 70,000 patients with CF worldwide, the prevalence of the target population is approximately 7.3% (3.5% with the *G551D* mutation; 2.8% with the *R117H* mutation; and 0.8% with non-*G551D* gating mutations).

Europe: Based on the European CF Society Patient Registry (ECFSPR) that included data on 48,204 patients with CF from 35 countries, the allelic frequency was 1.3% for *G551D* and 1.1% for *R117H*. For 2018, the UK CF Trust Registry reported that among 9,757 patients with genotyping, 5.9% had a *G551D* mutation.[9] In Ireland, among 2,474 patients with CF, 15.6% had a *G551D* mutation.[8]

US: In 2018, 1,347 (4.4%) patients had the *G551D* mutation and 924 (3.0%) patients had the *R117H* mutation.[4]

Canada: In 2017, 132 (3.1%) patients had a *G551D* mutation and 80 (1.9%) patients had the *R117H* mutation.[5]

Australia: In the ACFDR in 2017, 6.5% of patients had a *G551D* mutation and 3.1% of patients had an *R117H* mutation.[7]

SI.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Risk factors for the disease

CF is an autosomal recessive genetic disorder. To have CF, a person must inherit 2 defective *CF transmembrane regulator* (*CFTR*) genes (1 copy from each parent) resulting in the synthesis of dysfunctional CFTR protein.

Age at diagnosis

With increased rates of neonatal screening, the age at which CF is diagnosed is decreasing. The median age at the time of diagnosis was approximately 2, 4, and 2 months, as reported by the CF registries in UK[9], Ireland[8], and France[14], respectively. Across 35 countries that contributed data to ECFSPR in 2017, the median age at diagnosis was 4.0 months.[15]

Similarly, in the US in 2018, the median age at diagnosis was 3 months; 61.5% of patients were diagnosed by newborn screening.[4]

In Canada, newborn screening is performed in all provinces. In 2017, the majority (59.9%) of patients with CF were diagnosed by 1 year of age.[5]

In Australia, 55 of 72 new diagnoses in 2017 were made at less than 1 year of age; all but 1 was diagnosed by age 3 months.[7]

Age distribution among prevalent patients

Of the 48,204 CF patients from 35 countries in the ECFSPR (including non-EU member states) with a patient encounter in 2017, the median age was 18.5 years. Of the total population, 51.3% were older than 18 years of age.[15] In the UK 60.4% of CF patients were over the age of 16 years in 2018.[9]

In the US, 54.6% of all CF patients were adults 18 years or older.[9] Despite the gains in median survival, the age distribution remains markedly skewed to the young. While the age of US CF patients ranged from birth to a maximum age of 88.7 years, the median age was 19.3 years in 2018.[9]

In Canada, CF patients ranged from birth to more than 70 years old, with the median age being reported as 22.8 years. Overall, 60.9% of patients with CF were 18 years or older, with 15.2% being over the age of 40, and 0.5% over the age of 70.[5]

In Australia, CF patient age ranged from birth to more than 60 years old, with a median age of 19.6 years in 2017. Overall, 53.7% of all CF patients were 18 years or older.[7]

Sex

Commonly, women with CF have been described to have worse outcomes than men.[16-18]

Among CF children in Europe, a male preponderance exists at birth and persists; this is reflected at all ages.[19] In 2017, 52.6% in the ECFSPR were male.[15] For 2017/2018, similar percentages were reported in country-specific registries, the UK (53% male patients)[9], US (51.8%)[4], Canada (53.9%)[5], and Australia (53.7%).[7]

Race/ethnic origin

CF affects all racial and ethnic groups and is more common among Caucasians.[20] In the US, 93.5% of CF patients in 2018 were Caucasian, 4.7% were African American, and 3.7% were other races; overall, 9.4% identified as Hispanic.[4] Race is not reported by European registries.

SI.4 Main Existing Treatment Options

With the exception of drugs that target the CFTR function, such as Kalydeco (ivacaftor [IVA]), Orkambi (lumacaftor in combination with ivacaftor [LUM/IVA]), Symdeko/Symkevi (tezacaftor in combination with ivacaftor [TEZ/IVA]), and Trikafta/Kaftrio (elexacaftor/TEZ/IVA in combination with IVA), the main existing treatment options for CF comprise physiotherapy or drugs for the co-morbidities of CF, which may encompass the following:

Table 1 Main Existing Treatment Options in Patients With Cystic Fibrosis

CF lung disease	• Airway hydration (hypertonic saline) • Mucolytics (dornase alfa) • Oral antibiotics (amoxicillin clavulanate, ciprofloxacin, azithromycin, clarithromycin • Inhaled antibiotics (tobramycin, aztreonam, colistin) • IV antibiotics (ceftazidime, meropenem, piperacillin-tazobactam, tobramycin, amikacin) • Bronchodilators (albuterol, salmeterol) • Oxygen • Inhaled corticosteroids (budesonide, fluticasone) • Systemic corticosteroids (prednisolone, prednisone) • Chest physiotherapy
CF liver disease	• Oral bile acid therapy (ursodeoxycholic acid)
CFRD	• Insulin
CF related osteoporosis and osteopenia	• Vitamin D and calcium supplementation
Pancreatic insufficiency (PI) / malnutrition	• Pancreatic enzyme replacement • Acid reduction therapy (H2-blockers, proton-pump inhibitors) • Supplementation of fat-soluble vitamins A, D, E, and K • Appetite stimulation (hydroxyzine, cyproheptadine, megestrol acetate, dronabinol)
CF arthropathy	• Systemic corticosteroids (prednisolone, prednisone) • Methotrexate • TNF blockers, TNF receptor blockers
Anxiety and depression	• Anxiolytics • Antidepressants
Cardiac disease	• Digitalis and tolazoline hydrochloride have been reported as treatments for heart failure secondary to CF; however, no clear benefit of these treatments has been identified and they remain controversial.[21]

Table 1 Main Existing Treatment Options in Patients With Cystic Fibrosis

CF: cystic fibrosis; CFRD: cystic fibrosis related diabetes; IV: intravenous; PI: pancreatic insufficiency; TNF: tumor necrosis factor.

SI.5 Natural History of the Indicated Condition in the Untreated Population

Mortality in the target indication

The ECFSPR reported the median age at death was 29.0 years in 2017.[15] The EuroCareCF (2007 to 2009)-reported median age at death for 14 European countries was between 18.7 years in Poland and 33.0 years in the Netherlands, with the exception of Macedonia where the median age at death was 9.5 years.[2] Female survival disadvantage exists.[22]

CF mortality in children 5 years of age or younger is low. Available data from patient registries in 2017/2018 approximates mortality to be significantly <1%.

A patient with CF born in the last 2 decades of the 20th century (in an economically developed nation) is now expected to have a greater-than-50% chance of survival to 40 years of age.[19] In an international cohort of 366 patients with CF aged 40 years or older from Canada, UK, US, and Italy, the estimated annual mortality rate was 3.4%.[16]

The reported median age at death, median predicted survival, and mortality rates across selected European countries, the US, Canada, and Australia are summarised as follows:

Country, Year	Median age at death (years)	Median predicted survival (years)	Annual Mortality rate
UK, 2018[9]	32.0	47.3	1.3%
Ireland, 2017[8]	32.0	45.7	1.2%
France, 2016[14]	28.0	n/a	0.8%
Germany, 2016[23]	33.0	n/a	1.1%
US, 2018[9]	30.8	47.4	1.3%
Canada, 2017[5]	33.6	52.3	1.0%
Australia, 2017[7]	35.6	n/a	0.6%

n/a: not available

Although McKone et al. showed that CF patients with *F508del/R117H-CFTR* had a significantly lower mortality rate than those who were homozygous for *F508del*, there are no data on the mortality of patients with CF who have the *R117H* mutation by poly-T tract variant.[4,5,8,9,24]

Morbidity

While mutations in the *CFTR* gene affect secretory glands, the most affected organs are lungs, pancreas, liver/gallbladder, intestines, sinuses, vas deferens, and sweat glands. Other complications of CF include CF-related diabetes (CFRD), bone disease, CF-related arthropathy, and anxiety and depression.

SI.6 Important Comorbidities

The important comorbidities of CF include CF lung disease, CF liver disease (CFLD), CFRD, CF-related osteoporosis and osteopenia, pancreatic insufficiency (PI)/malnutrition, anxiety and depression, and cardiac disease.

SI.6.1 CF Lung Disease

CF lung disease is the most prevalent manifestation of CF. The natural history of CF lung disease is one of chronic airway infection and gradual progression driven by intermittent

episodes of acute pulmonary exacerbations. This progression typically starts with mucus plugging of peripheral airways and concomitant air trapping. Retained mucus plugs and plaques within the airway serve as a nidus of chronic infection by certain pathogens, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa,* which are particularly well adapted to surviving in retained airway secretions. Inflammation and scarring associated with this chronic airway infection results in bronchial wall thickening and progressive bronchiectasis. Recent studies indicate that the episodes of acute pulmonary exacerbation, representing infectious flares, drive these later stage findings, reflecting overall lung disease progression.

In 2018, 44.4% of US CF patients had at least 1 positive culture for *P aeruginosa* as characterised by the Leeds criteria*,* with 28.3% being categorised as having chronic infection and 17.0% as intermittent infection. For methicillin-resistant *S aureus, Burkholderia cepacia complex, S aureus*, the prevalence was 25.0%, 2.6%, and 70.3%, respectively.[4] Pulmonary infection is the most pronounced clinical issue and the progressive pulmonary dysfunction is the main prognostic factor for patients with CF.

According to the 2017 report from the CF Registry of Ireland, 34.6% of patients had at least 1 pulmonary exacerbation requiring intravenous (IV) antibiotics; 24.4% of children (<18 years, n=130) and 42.3% of adults (≥18 years; n=298).[8] In 3 studies of children and adults with CF that used computed tomography (CT) to detect lung disease, bronchiectasis was the most common lung abnormality. In cohorts in Italy, Austria, and the Netherlands, bronchiectasis was identified in 89%, 80%, and 76% of patients, respectively; similarly, bronchial wall thickening was identified in 48%, 76%, and 85% of patients with CF, respectively. Mucous plugging was identified in 29%, 51%, and 79%, respectively.[25-27] The relative prevalence of CT findings in these populations reflects the sampling of relatively older CF patients in these studies.

Lung disease severity tends to increase with age among those with moderate and poor lung function.[4]

CF lung disease is characterised by progressive airway obstruction as measured by percent predicted forced expiratory volume in 1 second ($ppFEV_1$). In the 2017 ECFSPR report, the median $ppFEV_1$ for patients who have never had a lung transplant was 97.3 for aged 6 to 9 years, declining through the adolescent (90.7 for aged 10 to 14 years, and 83.0 for 15 to 19 years) and adult years (including 75.1 for aged 20 to 24 years and 62.4 for 45 years and older).[15] Taken together, these values reflect progressive lung disease from the earliest age at which lung function is measurable. Similar trends were observed in data from registries in the UK[9], Ireland[8], Germany[23], Canada[5], and Australia[7].

Based on 2018 US CFFPR report, median $ppFEV_1$ was 94.3 for patients aged 6 to 17 years and 69.4 for patients aged 18 years and older[4], suggesting that in aggregate, US CF patients in a given age cohort generally have less airway obstruction (and thus, less severe lung disease) than their European counterparts.

Lung disease is the most serious complication of CF, causing the majority of mortality in patients with CF. Respiratory and/or cardiorespiratory complications was the primary cause of death for 59.3% and 66.5% of deaths for patients with CF in the US and EU patient registries, respectively.[4,15]

SI.6.2 CF Liver Disease

While there is no standard, universally-accepted definition of what constitutes CFLD, the literature is generally in agreement that the majority of CF patients will at some time have evidence of a wide range of liver abnormalities, including those in liver biochemistry, changes in appearance by ultrasound or other abnormalities as follows:[28-31]

Liver Abnormalities in Cystic Fibrosis Patients	
Hepatic abnormalities	
Asymptomatic liver function test elevations	Common (estimates vary widely)
Hepatomegaly	Common (estimates vary widely)
Steatosis and steatohepatitis	Common (23% to 67%)
Neonatal cholestasis	Not common (<2%)
Focal biliary cirrhosis	Common (11% to 72%)
Multilobular cirrhosis	Less common (up to 15%)
Portal hypertension	Less common (up to 5%)
Synthetic liver failure	Rare
Biliary abnormalities	
Microgallbladder	Common (30%)
Cholelithiasis and cholecystitis	Less common (up to 15%)
Bile duct stenosis	Not common (<2%)
Sclerosing cholangitis	Not common (<1%)
Cholangiocarcinoma	Rare

As defined by a combination of any 2 signs (i.e., hepatomegaly/splenomegaly, increased liver function tests (LFTs), and/or ultrasound), the cumulative incidence of CFLD based on long-term follow-up was 18% in the US, 27% in Italy, and 28% in Israel.[29,32,33]

The incidence rate of CFLD was reported as 3.61 per 100 person-years (PY) in a cohort in Montreal, Canada, and 1.8 per 100 PY in a cohort from Milan, Italy.[33,34]

Liver function test abnormalities

Liver abnormalities are very common among CF infants with up to 53% having elevated LFTs by 3 years of age.[35] In 2 large CF patient registries in UK (2018) and Australia (2017), prevalence of abnormal LFTs in the overall CF population (all ages) was reported at 9.0% and 10.2%, respectively.[7,9]

Based on the analysis of data from 376 participants of 3 multi-centre CF studies with an average follow-up of 8.3 months, the incidence rate for developing: any alanine aminotransferase (ALT) increase was 2 per 100 person-months, any LFT abnormality was 3.4 per 100 person-months, and any clinically significant LFT abnormality was 0.4 per 100 person-months.[36]

If followed for 5 to 10 years, approximately 35% to 50% of CF patients would have LFT elevations on at least 1 occasion,[33,34] with up to 93% of patients with LFT abnormalities over 20 years of follow-up.[37]

Of note, while transient or even persistent LFT increases are frequent in CF, they have a low sensitivity and specificity in predicting clinically significant CFLD. For instance, in 1 study among patients with abnormal liver enzyme testing, 25% went on to develop CFLD during follow-up (mean of 8 years).[32]

Clinically significant liver disease

While biochemical or ultrasound liver abnormalities are commonly observed in CF patients, clinically significant CFLD (such as multilobular cirrhosis and/or portal hypertension) affects a much smaller percentage of the CF population.

The literature suggests that up to 10% of patients with CF develop cirrhosis, with most of these patients having signs of portal hypertension.[33,35,38] The prevalence of cirrhosis in the CF population was 3.3% in the US[4], 0.7% (without portal hypertension) and 1.1% (with portal hypertension) in the UK[9], 2.1% (cirrhosis or portal hypertension) in Australia.[7]

Two prospective studies[33,34] reported sufficient data to estimate the incidence rates of clinically significant liver disease. Using the reported case counts and person-time from these 2 studies, the rates were estimated at:

- 7 to 8 per 1,000 patient years for cirrhosis,
- 5.3 to 5.5 per 1,000 patient-years for cirrhosis with portal hypertension,
- 1.6 per 1,000 patient-years for cirrhosis with varices, and
- 3.4 per 1,000 patient-years for hepatic failure.

Liver disease, including liver failure, remains an important non-pulmonary cause of death, accounting for approximately 3.4% of overall CF mortality in the US[4] and 2.2% in the UK[9]. The ECFSPR reported 2.6% of all deaths to be liver-gastrointestinal related.[15]

During 7-year follow-up of 36 children with CFLD, 3 (8%) patients died from liver failure and 1 (3%) patient received a liver transplant. Another 3 (8%) patients with CFLD died from pulmonary failure. Overall, the mortality at 7 years was 19.4% in the cohort of patients with CFLD.[39]

SI.6.3 CF-Related Diabetes

CFRD increased with age with prevalence at 31% to 50% of adults.[40-42] For 2018, CF patient registries reported the prevalence of CFRD at

- 18.5% (5.3% in patients aged <18 years compared to 30.6% in patients aged ≥18 years) in the US[4].
- 26.6% (7.4% in patients aged 10 to 15 years compared to 31.1% in patients ≥16 years) in the UK[9], and
- 22.4% (3.1% children compared to 34.8% adults) in Canada.[5]

The annual incidence of CFRD was estimated at 3.8% in a Danish cohort[43], 3.5% in a British cohort[44], and 2.7% in a US cohort.[42] In the Danish study, the annual incidence increased with age at 5% per year for patients aged 10 years or older and 9.3% per year for patients aged 20 years or older.[43] In a Canadian cohort, 107 patients were diagnosed with CFRD over a 10-year period; resulting in a 2% annual incidence, with a 10-year prevalence of 24%.[45]

It is believed that CFRD causes more rapid decline in pulmonary function and nutrition status, particularly in female patients. There is also evidence that CFRD is associated with increased mortality.[46]

Data from the UK Cystic Fibrosis Registry showed that the age-adjusted mortality rate among patient with CFRD was 4.2 (95% CI: 3.4 to 5.1) per 100 person-years, whilst the rate in patients with CF but without CFRD was only 1.5 (95% CI: 1.3 to 1.7) per 100 person-years.[47]

SI.6.4 CF-Related Osteoporosis and Osteopenia

Bone mass is abnormally low in patients with CF, even when treatment includes large supplements of vitamin D and calcium.[48] Low bone mineral density was found even with calcium intake of 1200 or 1500 mg/day.[49-52] A meta-analysis of osteoporosis, osteopenia, and vertebral and non-vertebral fractures among adults with CF reported pooled prevalences of 23.5%, 38%, 14%, and 19.7%, respectively.[53]

Fractures are very common in patients with CF, and often more than 1 fracture occurs during the life of a patient with CF.[48] In studies, the fracture rate was increased 2-fold in women aged 16 to 34 years and in men aged 25 to 45 years, as compared to the general population.[52]

Kyphosis with an angle greater than 40° was diagnosed in 19% of patients with CF overall. These cases occurred in 77% of females and 36% of males over 15 years of age.[52,54]

In 2017/2018, the percentage of patients with CF with osteoporosis was 3.7% in the US, 4.7% in the UK, 13.9% in Ireland, and 3.2% in Australia; the percentage of patient with osteopenia was 10.0% in the US, 10.3% in the UK, 11.4% in Ireland, and 7.9% in Australia.[4,7-9]

SI.6.5 Pancreatic Insufficiency/Malnutrition

PI predisposing to fat malabsorption, steatorrhoea, and failure to thrive is present in greater than 90% of patients with CF and is often present at the time of diagnosis in the majority of patients who are diagnosed on the basis of symptoms. Patients diagnosed through newborn screening may not be symptomatic at the time of diagnosis; however, a significant proportion is PI at birth and early treatment with pancreatic enzymes and close attention to their nutritional management have been shown to result in improved growth.[55]

At CF diagnosis, patients are screened for exocrine pancreatic function using a combination of tests including 72-hour faecal fat balance, serum cationic trypsinogen assay, and direct assessment of pancreatic function by secretin-cholecystokinin stimulation.[56,57] However, research using prevalent cohorts of patients with CF often use evidence of use of pancreatic enzyme supplements to define PI.[40,41]

Most patients with CF with functionally severe mutations on both alleles have PI.[56] Among cohorts of patients with CF in Europe and the US, 72% to 90% had PI.[56,57] In Canada, 84.9% of patients with CF are PI and 15.3% are pancreatic sufficient.[5] In a cohort of patients with CF over 40 years of age in the UK, 82% had PI as identified in clinical notes.[58]

Deficiency in fat-soluble vitamins A, D, E, and K is a consequence of steatorrhoea.

SI.6.6 Anxiety and Depression

Estimates of prevalence of depression and anxiety in CF patients vary by the method of ascertainment, geography, and age.

In the US in 2018, a clinical diagnosis of depression was reported in 15.8% and anxiety disorder was reported in 13.5% of all CF patients.[4] Depression or anxiety was diagnosed in 12.6% of CF patients (4.7% in children and 17.6% in adults) in Canada in 2017[5], 3.8% of CF patients (0.2% in patients aged <16 years and 6.2% in patients ≥16 years) in the UK[9], and 4.6% of CF patients (0.4% in children and 7.8% in adults) in Ireland[8].

In 2014, Quittner et al. published results from a large international study across 154 centres in Europe and the US that screened for depression and anxiety in a sample of 6,088 CF patients, as well as a community sample of 4,102 caregivers who have children with CF. The prevalence of depressive symptoms was 2 times higher in the sample of CF patients compared to the community sample, highlighted in higher burden of these conditions in the CF population.[59]

Within this same study by Quittner et al., the sample of CF patients included 1,286 adolescents (aged 12 to 17 years) and 4,739 adults (aged ≥18 years). Depending on age and the screening tool used, rates of depression varied across countries, ranging from 5% to 19% in adolescents and 13% to 29% in adults. Furthermore, 4% of the adolescent patients with CF and 10% of the adult patients with CF reported currently taking a psychiatric

medication for depression/anxiety, while 6% of the adolescent CF patients and 8% of the adult CF patients reported currently receiving psychotherapy.[59]

In 2015, the CF Foundation and the European CF Society published recommendations for annual screening and treatment of depression and anxiety in all individuals with CF who are 12 years of age and older. As a steady increase is being observed in the number of patients screened for anxiety and depression, the prevalence of diagnosed anxiety and depression is also increasing over time.[4]

SI.6.7 Cardiac Disease

Cardiac disease as a result of progressive hypoxia due to severe lung disease is usually described as right ventricular dysfunction and cor pulmonale. Cor pulmonale, as defined by hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease,[60] has been reported for patients with CF since 1946. The prevalence of cor pulmonale has varied from 6% to 70% when based on postmortem studies.[61]

Heart failure has been reported at a prevalence of 8.3% among a cohort of patients with CF in Ohio, US.[21] Ischemic heart disease has not historically been reported for patients with CF. However, given the high-fat diet and comorbid CFRD, there is speculation that as more patients with CF live into adulthood there may be an increase in ischemic heart disease. A case report for the first symptomatic myocardial infarction in a patient with CF has been published.[62] However, there are no estimates for incidence or prevalence of ischemic heart disease.

Of 170 patients who died at a CF clinic in Ohio, US, 55 (32%) had overt right heart failure at least 2 weeks before death. Among 61 patients with CF and heart failure, the mean survival was 8 months with a median survival of 4 months.[21]

SII Nonclinical Part of the Safety Specification

SII.1 Toxicity

Acute and repeat dose toxicity

Ivacaftor (IVA) demonstrated a low potential for toxicity from high single doses in both mice (maximum tolerated dose [MTD] = 2000 mg/kg) and rats (MTD = 500 mg/kg). No IVA related adverse effects were seen at levels that represent 9 to 16 times the maximum recommended human dose (MRHD) on an exposure (AUC) basis at the recommended human therapeutic dose.

In repeat-dose studies of IVA with duration of up to 3 months in mice, 6 months in rats, and 12 months in dogs, the principal target organ of toxicity for IVA was the liver; this was observed only in rodent species. Dose-related elevations in liver weights (rats only) were accompanied by histologic changes in the liver (centrilobular hepatocellular necrosis with or without acute/subacute inflammation). These histological changes were observed at high dosages in a few animals in 3-month studies in the mouse (≥600 mg/kg/day) and rat (≥200 mg/kg/day). Clinical chemistry changes (alanine aminotransferase [ALT] and total bilirubin) without histologic findings were observed in the 6-month rat study (≥100 mg/kg/day). Hepatic accumulation of IVA and the resulting high liver-to-plasma concentration ratios (16:1, measured in the 3-month rat study) are believed to be a rodent-specific phenomenon of xenobiotic overload at high daily doses. This finding is supported by the lack of observations of hepatotoxicity or significant hepatic accumulation in dogs, where

liver-to-plasma concentration ratios were only 2:1 in the 3-month study despite the high daily doses and similar exposures to circulating ivacaftor at hepatotoxic dosages in rats and mice. The hepatotoxicity seen in rats and mice is considered to be related to a rodent-specific xenobiotic overload; the finding was not observed in dogs. In addition, the relative exposures at which the findings were observed in rats and mice are much higher than the expected exposures in humans.

The only noteworthy findings in dogs in repeat-dose studies were occasional instances of atrioventricular block, a well-documented background finding in this species. In addition, there was a slight increase in the incidence (3 of 40 dogs) of supraventricular premature complex (SVPC) runs, consisting of multiple events within a single electrocardiogram (ECG) recording, at dosages ≥30 mg/kg/day. The SVPCs were not associated with biochemical or morphological changes in the heart or changes in health status of the 3 dogs affected. The SVPCs resolved following the 1-month recovery period. Both ECG observations were considered related to canine-specific control of heart rates and therefore unlikely to translate clinically in humans. Nonetheless, 12-lead and ambulatory (holter) ECGs were assessed in the Phase 2b/3 studies to identify any potential for ECG abnormalities, including supraventricular ectopy or other abnormalities. In these studies, no evidence of arrhythmias and ectopy or evidence of abnormalities was noted in IVA -treated subjects compared with placebo. Cumulative data from the clinical development program, post-marketing experience, and results from the Long-term Safety Study (LTSS) were consistent and did not demonstrate an association between IVA treatment and cardiac arrhythmia.

In the chronic toxicity studies, IVA exposures at the no observed adverse effect level in rats (50 mg/kg/day) and dogs (60 mg/kg/day) were at least 9- to 18-fold higher than the estimated steady-state $AUC_{0\text{-}24h}$ (29.6 µg•hr/mL) at the recommended human therapeutic dose.

Developmental and reproductive toxicity

No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 6 and 3 times the MRHD based on summed AUCs of IVA and its metabolites). IVA impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 8 and 5 times, respectively, the MRHD based on summed AUCs of IVA and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. IVA also increased the number of female rats with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of IVA and its metabolites) when dams were given doses before and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity at this dose level, not direct effects on reproductive tissues.

Juvenile toxicity Study

Study VX-770-TX-025 was designed to assess the potential adverse effects on neonatal growth and development of repeated oral administration of ivacaftor in juvenile male and female rats when dosed from postnatal day (PND) 7 through PND 35.

Juvenile male and female Crl:CD(SD) rats (F0 pups, 20/sex/group main study animals, 45/sex/group toxicokinetics [TK] animals), obtained from naïve, time-mated females, were given doses of ivacaftor daily by oral administration at dose levels of 0 (controls), 10, 25, or 50 mg/kg/day. At the end of the dosing phase, half the surviving animals in each group were euthanized, with the remaining animals moving into a recovery phase (no further dosing), to be euthanized 28 days later.

Juvenile toxicity studies conducted in rats identified the eye (lens opacities/cataracts) as a key target organ of IVA-related toxicity; this finding has not been observed in fetuses derived from female rats treated on Gestation Day (GD) 7 to 17, in rat pups exposed to a certain extent through milk ingestion up to PND 20, or in repeat-dose toxicity studies using older animals at study initiation (i.e., 7 week-old rats, or 4- to 5-month-old dogs).

Lens opacities (cataracts) observed in the juvenile rat toxicity study were considered ivacaftor related, and all cataracts were located in the nucleus (center) portion of the lens. Because the lens nucleus is the oldest portion of the lens, with new fibers being added to the cortical (peripheral) area of the lens as it develops, the initiating event in the development of cataracts is believed to have occurred early in lens development relative to dosing.

Final histopathological analysis of ocular tissues originated from newborn rats exposed to IVA in the juvenile toxicity Study VX-770-TX-025 demonstrated no IVA-related microscopic findings in the eyes at the primary or recovery necropsies. The absence of lenticular degeneration associated with the cataracts observed and the deposition of new, presumably normal fibers in the developing lenses of these juvenile rats, suggest that permanent damage to the lens forming structures in the eye did not occur.

In the evaluation of retained heads from foetuses from the IVA embryo-foetal development (EFD) study, light microscopic examination performed on the eyes of male and female rat foetuses in the control and 200 mg/kg/day dosage groups revealed no treatment-related findings. There was no evidence of cataracts or lenticular degeneration in any of the eyes that were examined microscopically. Therefore, IVA given to pregnant rats during the organogenesis phase of foetal development (GD 7 through GD 17) had no effect on the development of foetal eye tissues.

Because no cataractogenic potential for ivacaftor was detected in repeat-dose studies conducted in older rats or dogs, the onset of lens opacities in newborn rats exposed to IVA was considered to be a developmentally dependent phenomenon that occurred because IVA was given through a critical stage of lens development in the newborn rats. Given the substantial developmental time-dependent differences in lens maturation between humans and rats reported in the literature, it is unlikely that the finding is relevant to humans 6 years of age and older. In younger children, particularly children <2 years of age, there may be a greater risk of cataract development, but this is still uncertain, given the cited differences in human and rat lens development.

Genotoxicity

IVA was shown to be non-mutagenic and non-clastogenic in the following standard in vivo and in vitro genotoxicity tests: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test.

Carcinogenicity

Lifetime (2-year) dosing studies in both rats and mice have shown that IVA is not carcinogenic at the highest dosages tested (200 mg/kg/day in mice, 50 mg/kg/day in rats). At these dose levels, steady-state exposures to IVA were in excess (4- to 29-fold) of the projected human steady-state exposure to ivacaftor at the therapeutic dosage (150 mg q12h). Lifetime studies in rodents are accepted models for predicting carcinogenic potential in humans, and thus the animal toxicity studies do not suggest an increased carcinogenicity risk in humans.

SII.2 Safety Pharmacology

IVA has been studied extensively in GLP-compliant, nonclinical studies to determine its pharmacological activity, metabolism, pharmacokinetics (PK), and safety.

In vitro off-target effects

IVA was evaluated in vitro for off-target effects on a wide variety of receptors and enzymes in radioligand binding assays, as well as for interactions with a variety of ion channels including the human ether-à-go-go-related gene-encoded channel (hERG), a standard system used to evaluate the potential risk of drug-induced QT prolongation. IVA did not potently bind to or alter the function of these targets, indicating a low potential for off-target effects. Consistent with the in vitro data showing a lack of hERG activity, there were no effects on QTcF observed in dogs, even at high doses of ivacaftor.

A panel of exploratory binding affinity studies evaluating the potential for secondary pharmacodynamic (PD) effects associated with IVA, demonstrated a low potential for off-target effects that could result in untoward effects at therapeutic exposures. When evaluated for off-target effects in a large panel of in vitro receptor, channel, and enzyme radioligand binding assays, M6 (a major human metabolite of ivacaftor) was found to have a low potential for off-target or secondary PD effects as determined by its lack of significant binding affinity in any of the >180 assays conducted.

Pharmacokinetics

M1 and M6 were major circulating metabolites in all species studied, and M1 was found to be pharmacologically active in vitro (1/6th of the potency of IVA), whereas M6 was inactive (<1/50th of the potency of IVA). Systemic exposures to major human metabolite M6 in rats and dogs were lower than relative human exposures to this metabolite at the intended therapeutic dose level of IVA.

Placental transfer of ^{14}C-labelled IVA occurred after a single oral dose to pregnant rats and rabbits, but the exposures to ivacaftor in foetuses were low and variable. ^{14}C-labelled IVA accumulated in the milk of pregnant and lactating rats.

It is not known whether this finding in pregnant or lactating rats translates to humans. The clinical significance of the finding to humans is unknown.

Mechanisms for drug interactions

In vitro studies indicated that IVA is a substrate of cytochrome P450 (CYP) 3A, an inhibitor of permeability glycoprotein (P-gp), a potential inhibitor of cytochrome P450 (CYP) 2C8, 2C9, and 3A, and may be a metabolism-dependent inhibitor of CYP2D6. Clinical studies were conducted with inhibitors and inducers of CYP3A and with sensitive substrates of CYP2C8, CYP3A, CYP2D6 and P-gp. Because no drug-drug interaction (DDI) was observed clinically, between ivacaftor and rosiglitazone, a CYP2C8 probe, and coupled with the in vitro K_i for CYP2C9 being 10-fold higher than that for CYP2C8, no interaction with CYP2C9 is expected and so was not studied further. However, based on the in vitro results with CYP2C9, a recommendation for monitoring international normalised ratio (INR) is recommended in the Summary of Product Characteristics (SmPC) when co-dosing with warfarin.

SII.3 Other Toxicity-Related Information or Data

Based on the discussion in Sections SII.1 and SII.2, further nonclinical studies are not warranted. Safety concerns from the nonclinical data include the effect of ivacaftor on

hepatotoxicity (transaminase elevation), cataract, drug interactions with strong CYP3A inhibitors or inducers, and cardiac arrhythmias; and ivacaftor placental transfer and presence in breast milk.

SIII Clinical Trial Exposure

This section summarises the cumulative subject exposure data since the Development International Birth Date (DIBD; 13 April 2006) in all clinical studies sponsored by the MAH. Data from non-interventional studies, including compassionate-use programmes, are included in the postmarketing section (Section SV).

As of 23 January 2024, a total of 1,727 subjects have been exposed to at least 1 dose of IVA in monotherapy clinical studies. As shown in Table 2 (presented by dose) and Table 3 (presented by duration), 1,158 were subjects with CF (1,097.7 PY exposure) and 569 were healthy subjects (11.2 PY).

The cumulative subject exposure by age, sex, and racial group are provided in Table 4, Table 5 and Table 6, respectively. The [redacted] of subjects exposed to IVA monotherapy were 18 years of age and older (1,325 subjects), [redacted]. Among the pediatric subjects, a total of 186 subjects 12 to <18 years of age, 84 subjects 6 to <12 years of age, 52 subjects 2 to <6 years of age, 51 subjects 12 to <24 months of age, 54 subjects 6 to <12 months of age, and 22 subjects <6 months of age received IVA.

Table 2 Summary of Cumulative Exposure in Clinical Studies With IVA by Dose

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Dose	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**
Total	**600**	**15.9**	**1,295**	**1,251.2**	**1,895**	**1,267.0**
IVA (Any Formulation)	**569**	**11.2**	**1,158**	**1,097.7**	**1,727**	**1,108.0**
IVA (Tablet[c])	**569**	**11.2**	**1,022**	**882.4**	**1,591**	**893.5**
IVA 150 mg	463	8.2	1,002	880.4	1,465	888.5
IVA 250 mg	32	1.0	7	0.5	39	1.5
IVA 450 mg	76	1.0	0	NA	76	1.0
Other IVA	138	1.0	32	1.4	170	2.5
IVA (Granule)	**0**	**NA**	**147**	**215.4**	**147**	**215.4**
IVA <25 mg	0	NA	7	1.4	7	1.4
IVA 25 mg	0	NA	21	2.7	21	2.7
IVA 50 mg	0	NA	105	128.9	105	128.9
IVA 75 mg	0	NA	81	82.4	81	82.4
Placebo (Any Formulation)	**159**	**4.7**	**477**	**153.4**	**636**	**158.1**

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; NA: not applicable; PY: patient-years; patient-days are displayed if drug exposure is ≤36 days.

Notes: N: Number of subjects in the Safety Set (who have received any amount of IVA or placebo) and had dosing information included in the clinical database by 23 January 2024. A subject may be included in multiple IVA dose rows, but only counted once in the treatment/treatment dose form/total rows.

[a] Includes studies with completed CSRs: 770 (001 Parts A, B, C, and E, 002, 003, 005-013, and 015-018), 809 (005 and 006), and 659 (001 Part B and 006 Part D), and 117-001. Also, 12 subjects with hepatic impairment from study 770-113 were mapped to the Healthy Subject columns while on 150 mg IVA.

[b] Includes completed studies [770 (001 Part D, 101-113, 123, 124, 126, and 127), PS-G202, 661 (108, 109, and 115), 445-104, and 561-101].

[c] Includes solution formulation used in Phase 1 studies.

Table 3 Summary of Cumulative Exposure in Clinical Studies With IVA by Duration

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Duration	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**
Total	600	15.9	1295	1251.2	1895	1267.0 (PY)
1 day	79	0.2	4	4.0 (PD)	83	0.2
>1 day to <4 weeks	494	11.8	58	2.8	552	14.6
≥4 to < 8 weeks	27	3.8	256	25.3	283	29.2
≥8 to <24 weeks	0	NA	485	121.2	485	121.2
≥24 to <48 weeks	0	NA	34	23.4	34	23.4
≥48 to <72 weeks	0	NA	50	59.6	50	59.6
≥72 to <96 weeks	0	NA	53	83.2	53	83.2
≥96 weeks	0	NA	355	935.6	355	935.6
IVA	**569**	**11.2**	**1,158**	**1,097.7**	**1,727**	**1,108.9**
1 day	79	0.2	2	2.0 (PD)	81	0.2
>1 day to <4 weeks	477	9.9	58	3.0	535	13.0
≥4 to < 8 weeks	13	1.0	252	24.5	265	25.5
≥8 to <24 weeks	0	NA	364	81.2	364	81.2
≥24 to <48 weeks	0	NA	29	18.5	29	18.5
≥48 to <72 weeks	0	NA	60	71.3	60	71.3
≥72 to <96 weeks	0	NA	71	116.5	72	116.5
≥96 weeks	0	NA	322	782.7	322	782.7
Placebo	**159**	**4.7**	**477**	**153.4**	**636**	**158.1**
1 day	27	27.0 (PD)	2	2.0 (PD)	29	29.0 (PD)
>1 day to <4 weeks	118	3.6	20	1.1	138	4.7
≥4 to <8 weeks	14	1.1	125	14.7	139	15.8
≥8 to <24 weeks	0	NA	212	40.5	212	40.5
≥24 to <48 weeks	0	NA	58	41.2	58	41.2
≥48 to <72 weeks	0	NA	60	55.9	60	55.9
≥72 to <96 weeks	0	NA	0	NA	0	NA
≥96 weeks	0	NA	0	NA	0	NA

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; NA: not applicable; PY: patient-years; patient-days are displayed if drug exposure is ≤36 days

Notes: N: Number of subjects in the Safety Set (who have received any amount of IVA or placebo) and had dosing information included in the clinical database by 23 January 2024.

A subject may be included in multiple IVA dose rows, but only counted once in the treatment/treatment dose form/total rows.

[a] Includes studies with completed CSRs: 770 (001 Parts A, B, C, and E, 002, 003, 005-013, and 015-018), 809 (005 and 006), and 659 (001 Part B and 006 Part D), and 117-001. Also, 12 subjects with hepatic impairment from study 770-113 were mapped to the Healthy Subject columns while on 150 mg IVA.

[b] Includes completed studies [770 (001 Part D, 101-113, 123, 124, 126, and 127), PS-G202, 661 (108, 109, and 115), 445-104, and 561-101].

Table 4 Summary of Cumulative Exposure in Clinical Studies With IVA by Age

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Age	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**
Total	**600**	**15.9**	**1,295**	**1,251.2**	**1,895**	**1,267.0**
≥1 to <4 months	0	NA	9	3.0	9	3.0
≥4 to <6 months	0	NA	13	8.3	13	8.3
≥6 to <12 months	0	NA	54	66.5	54	66.5
≥12 to <24 months	0	NA	51	69.3	51	69.3
≥2 to <6 years	0	NA	53	76.6	53	76.6
≥6 to <12 years	0	NA	91	160.9	91	160.9
≥12 to <18 years	0	NA	209	179.2	209	179.2

Table 4 Summary of Cumulative Exposure in Clinical Studies With IVA by Age

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Age	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**
≥18 to <65 years	600	15.9	856	682.5	1,456	698.4
≥65 years	0	NA	10	5.0	10	5.0
≥18 years	600	15.9	866	687.5	1,466	703.4
IVA	**569**	**11.2**	**1,158**	**1097.7**	**1,727**	**1108.9**
≥1 to <4 months	0	NA	9	3.0	9	3.0
≥4 to <6 months	0	NA	13	8.3	13	8.3
≥6 to <12 months	0	NA	54	66.5	54	66.5
≥12 to <24 months	0	NA	51	69.3	51	69.3
≥2 to <6 years	0	NA	52	74.6	52	74.6
≥6 to <12 years	0	NA	84	134.8	84	134.8
≥12 to <18 years	0	NA	186	154.1	186	154.1
≥18 to <65 years	569	11.2	750	583.4	1319	594.6
≥65 years	0	NA	6	3.9	6	3.9
≥18 years	569	11.2	756	587.3	1325	598.5
Placebo	**159**	**4.7**	**477**	**153.4**	**636**	**158.1**
≥1 to <4 months	0	NA	0	NA	0	NA
≥4 to <6 months	0	NA	0	NA	0	NA
≥6 to <12 months	0	NA	0	NA	0	NA
≥12 to <24 months	0	NA	0	NA	0	NA
≥2 to <6 years	0	NA	13	2.0	13	2.0
≥6 to <12 years	0	NA	53	26.1	53	26.1
≥12 to <18 years	0	NA	73	25.1	73	25.1
≥18 to <65 years	159	4.7	332	99.0	491	103.8
≥65 years	0	NA	6	1.1	6	1.1
≥18 years	159	4.7	338	100.2	497	104.9

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; NA: not applicable; PY: patient-years; patient-days are displayed if drug exposure is ≤36 days

Notes: N: Number of subjects in the Safety Set (who have received any amount of IVA or placebo) and had dosing information included in the clinical database by 23 January 2024.

A subject may be included in multiple IVA dose rows, but only counted once in the treatment/treatment dose form/total rows.

[a] Includes studies with completed CSRs: 770 (001 Parts A, B, C, and E, 002, 003, 005-013, and 015-018), 809 (005 and 006), and 659 (001 Part B and 006 Part D), and 117-001. Also, 12 subjects with hepatic impairment from study 770-113 were mapped to the Healthy Subject columns while on 150 mg IVA.

[b] Includes completed studies [770 (001 Part D, 101-113, 123, 124, 126, and 127), PS-G202, 661 (108, 109, and 115), 445-104, and 561-101].

Table 5 Summary of Cumulative Exposure in Clinical Studies With IVA by Sex

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Sex	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**	**N**	**Exposure (PY)**
Total	**600**	**15.9**	**1,295**	**1,251.2**	**1,895**	**1,267.0**
[redacted]						
IVA	**569**	**11.2**	**1,158**	**1,097.7**	**1,727**	**1,108.9**
[redacted]						
Placebo	**159**	**4.7**	**477**	**153.4**	**636**	**158.1**
[redacted]						

Table 5 Summary of Cumulative Exposure in Clinical Studies With IVA by Sex

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Sex	N	Exposure (PY)	N	Exposure (PY)	N	Exposure (PY)
[redacted]						

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; NA: not applicable; PY: patient-years; patient-days are displayed if drug exposure is ≤36 days

Notes: N: Number of subjects in the Safety Set (who have received any amount of IVA or placebo) and had dosing information included in the clinical database by 23 January 2024.

A subject may be included in multiple IVA dose rows, but only counted once in the treatment/treatment dose form/total rows.

[a] Includes studies with completed CSRs: 770 (001 Parts A, B, C, and E, 002, 003, 005-013, and 015-018), 809 (005 and 006), and 659 (001 Part B and 006 Part D), and 117-001. Also, 12 subjects with hepatic impairment from study 770-113 were mapped to the Healthy Subject columns while on 150 mg IVA.

[b] Includes completed studies [770 (001 Part D, 101-113, 123, 124, 126, and 127), PS-G202, 661 (108, 109, and 115), 445-104, and 561-101].

Table 6 Summary of Cumulative Exposure in Clinical Studies With IVA by Race

	Healthy Subjects[a]		Subjects With CF[b]		Overall[c]	
Race	N	Exposure (PY)	N	Exposure (PY)	N	Exposure (PY)
Total	**600**	**15.9**	**1,295**	**1,251.2**	**1,895**	**1,267.0**
[redacted]						
IVA	**569**	**11.2**	**1,158**	**1,097.7**	**1,727**	**1,108.9**
[redacted]						
Placebo	**159**	**4.7**	**477**	**153.4**	**636**	**158.1**
[redacted]						

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; NA: not applicable; PY: patient-years; patient-days are displayed if drug exposure is ≤36 days

Notes: N: Number of subjects in the Safety Set (who have received any amount of IVA or placebo) and had dosing information included in the clinical database by 23 January 2024.

[redacted]

[a] Includes studies with completed CSRs: 770 (001 Parts A, B, C, and E, 002, 003, 005-013, and 015-018), 809 (005 and 006), and 659 (001 Part B and 006 Part D), and 117-001. Also, 12 subjects with hepatic impairment from study 770-113 were mapped to the Healthy Subject columns while on 150 mg IVA.

[b] Includes completed studies [770 (001 Part D, 101-113, 123, 124, 126, and 127), PS-G202, 661 (108, 109, and 115), 445-104, and 561-101].

SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Acute upper or lower respiratory infections, pulmonary exacerbation, or changes in therapy for pulmonary disease within 4 weeks before Day 1	
Reason for exclusion	Acute respiratory infections or any adverse pulmonary conditions may alter the results of clinical studies.
Is it to be considered missing information?	No
Rationale	IVA does not show unfavourable effects on conditions described in the exclusion criterion. Ivacaftor improves overall pulmonary condition (ppFEV$_1$) of patients with CF.
Pregnancy, planning of pregnancy, or lactation	
Reason for exclusion	As a standard precautionary measure, pregnant and lactating women were excluded from clinical studies.
Is it to be considered missing information?	Yes
Rationale	The nonclinical studies suggest that IVA is not teratogenic at doses up to 3 × the maximum recommended human dose. Use of IVA in pregnancy and during lactation is considered missing information.
Abnormal liver function	
Reason for exclusion	The syndrome of CF-related diseases commonly includes changes to hepatic function, usually manifesting as chronic hepatobiliary disease. As a precautionary measure, subjects with abnormal liver function at screening were excluded from clinical studies.
Is it to be considered missing information?	Yes
Rationale	See Sections SVII.1.2.13. Safety of IVA use in patients with severe hepatic impairment represents missing information of IVA therapy.
Abnormal renal function	
Reason for exclusion	Renal impairment is not a common comorbidity of CF but, when present, is usually end stage secondary to frequent use of aminoglycosides. Patients with a history of abnormal renal function were excluded from clinical studies.
Is it to be considered missing information?	No
Rationale	As the renal route of elimination is negligible for IVA, with minimal excretion of IVA and metabolites, the use of IVA in patients with renal impairment is not contraindicated or considered missing information. In the SmPC, caution is recommended whilst using Kalydeco in patients with severe renal impairment or end-stage renal disease.
History of prolonged QT/QTcF interval (>450 ms)	
Reason for exclusion	The theoretical risk and nonclinical data suggest that ivacaftor might cause cardiac arrhythmias. As a precautionary measure, patients with history of prolonged QT were excluded from clinical studies.
Is it to be considered missing information?	No
Rationale	The potential risk of cardiac arrhythmias is based purely on theoretical data and nonclinical observations. Clinical experience did not confirm the relevance of this risk in humans. Therefore, there is no need for contraindication in patients with history of prolonged QT interval. However, the use of IVA in patients with cardiac diseases is missing information.
History of solid organ or haematological transplantation	
Reason for exclusion	CF patients with transplanted organs (e.g., lungs, heart, liver) were excluded from studies because these patients have significantly different baseline characteristics in terms of disease severity, concomitant therapy, and, in particular, immunosuppression. Patients with CF who have undergone lung transplantation were excluded from clinical studies with IVA because the transplanted lungs have normal CFTR.
Is it to be considered missing information?	No
Rationale	This has been adequately described in the labels that Kalydeco use in transplanted patients is not recommended.

Colonisation with organisms associated with a more rapid decline in pulmonary status	
Reason for exclusion	Conditions described in this exclusion criterion as any other pulmonary-related adverse conditions may interfere with study results.
Is it to be considered missing information?	No
Rationale	IVA does not show unfavourable effects in patients with bacteria in sputum. IVA improves overall pulmonary condition ($ppFEV_1$) of CF patients.
Subjects taking any inhibitors or inducers of CYP3A, including consumption of herbal medications and grapefruit/grapefruit juice	
Reason for exclusion	IVA is a sensitive CYP3A substrate. Inhibitors or inducers of CYP3A may modify the exposure of IVA and alter study results.
Is it to be considered missing information?	No
Rationale	Potential interactions with CYP3A inducers or inhibitors are adequately described in the label. Despite the recommended alteration of posology when co-administrating these substances with IVA, there is no need to contraindicate such combinations.
Evidence of cataract or lens opacity at screening	
Reason for exclusion	Cataract findings in the juvenile rats study.
Is it to be considered missing information?	No
Rationale	Given the substantial developmental time-dependent differences in lens maturation between humans and rats reported in the literature, it is unlikely that the finding is relevant to humans 6 years of age and older. However, cataracts is considered an important potential risk (see Sections SVII.1.2.2and SVII.3.1.2)

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator protein; CYP: cytochrome P450; IVA: ivacaftor; $ppFEV_1$: percent predicted forces expiratory volume in 1 second; ULN: upper limit of normal

SIV.2 Limitations to Detect Adverse Drug Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Pregnant women were not included in the clinical development programme. Use in pregnant women is considered missing information.
Breastfeeding women	Breastfeeding women were not included in the clinical development programme. Use in breastfeeding women is considered missing information.
Patients with hepatic impairment	As there is limited information in patients with Child-Pugh Class B and studies have not been conducted in subjects with severe hepatic impairment (Child-Pugh Class C), the safety in patients with moderate or severe hepatic impairment is considered missing information.
Patients with renal impairment	Subjects with renal impairment were not included in the clinical development programme. Renal impairment is not a common comorbidity of CF, but when present is usually end stage secondary to frequent use of aminoglycosides, or at the time of lung transplantation, when other nephrotoxic drugs must be used. Following oral administration, the majority of IVA (86.1%) is excreted in the feces after metabolic conversion. The major metabolites, M1 and M6, accounted for approximately 65% of the total dose excreted with 22% as M1 and 43% as M6. Urinary excretion of IVA as unchanged parent was negligible (<0.01%) and was minimal for IVA plus metabolites, 6.6% of the dose. As the renal route of elimination is negligible for IVA, with minimal excretion of IVA and metabolites, the use of IVA in patients with renal impairment does not represent a potential risk or missing information.

Type of Special Population	Exposure
Patients with cardiovascular impairment	No studies were performed to evaluate the safety of IVA in patients with cardiac diseases. Patients with CF are not known to have any increased incidence or prevalence of intrinsic cardiac disease. Any such cardiac symptomatology is usually secondary to other CF pathophysiology, particularly pulmonary disease. The use in patients with cardiac diseases is considered as missing information, and the risk of cardiac arrhythmias is included as an important potential risk.
Patients with a disease severity different from inclusion criteria in clinical trials	The Phase 3 studies enrolled subjects with mild or moderate lung function, generally represented as $ppFEV_1$ of 40 to 90. The pattern of AEs was similar across the subgroups by severity of lung disease, and the most common AEs within each FEV_1 subgroup were common manifestations of CF. As expected, subjects with more severe disease had a higher incidence of AEs compared to other subgroups, but IVA was well tolerated even in this most severely compromised group. Together, the information from clinical studies, compassionate-use programs, the LTSS, published literature, and post-marketing experience indicates that IVA treatment in patients with $ppFEV_1$ <40 have comparable treatment effects as in patients with $ppFEV_1$ ≥40.[63-65] No specific risks were identified in this patient group and the benefit risk balance appears to be favorable.
Population with relevant different ethnic origin	CF is a disease occurring primarily in Caucasians, and the population studied in the clinical studies was racially and ethnically representative of the CF population in general. Given the homogeneity of the CF population and the size of the safety database, population with different ethnic origin is not considered missing information.
Subpopulations carrying relevant genetic polymorphisms	Genetic polymorphism was not a consideration for enrollment in the clinical development programme and is not considered missing information.
Other	
Children aged less than 6 years	Given the limited number of subjects evaluated in clinical studies, use in children aged less than 6 years is considered missing information.
Elderly patients	The oldest subject with CF in the Phase 3 studies was aged [redacted] years. However, the effect of IVA in geriatric subjects has not been thoroughly evaluated. Given the current life expectancy of patients with CF, there are very few individuals with CF who live longer than 65 years. Whilst this may change through continued improvements in care, the absence of an evaluation of the effects of IVA in geriatric patients is currently not considered missing information, given the age profile of the current CF population.
Patients with relevant comorbidities	The signs and symptoms of CF occur in many body systems and organs. CF lung disease is the primary cause of morbidity and mortality in CF. The most common comorbid conditions associated with CF include CFLD, CFRD, osteoporosis and osteopenia, PI, depression, and cardiac disease. These conditions are described in Section SI.6. The clinical development programme included patients with relevant comorbidities, and it is considered that all important subpopulations of the CF patients have been exposed to the product in the clinical development programme.
Patients after organ transplant	Patients with CF who have undergone lung transplantation were excluded from clinical studies with ivacaftor as the transplanted lungs have normal CFTR, so they are not expected to benefit from ivacaftor treatment with respect to their lung disease. No specific safety concerns are expected in patients with organ transplant. The lack of clinical study evidence coming from this population is not considered to be missing information.

AE: adverse event; CF: cystic fibrosis; CFLD: cystic fibrosis liver disease; CFRD: cystic fibrosis-related diabetes; IVA: ivacaftor; LTSS: Long-term Safety Study; PI: pancreatic insufficiency $ppFEV_1$: percent predicted forced expiratory volume in 1 second

SV Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Cumulative post-authorisation exposures were estimated using data at the time of distribution, not necessarily the time of usage. There might be a delay between the time a medication was distributed and the time a medication was used by a patient. Caution must be

exercised when using post-authorisation exposure estimates to evaluate spontaneous reports. The methodology used for estimating post-authorisation exposure varies by geographic region as described below. Exposure estimates include both tablet and granule sachet formulations, based on approval status.

European Economic Area (EEA), Great Britain (GB), Australia, Switzerland, Israel, New Zealand, Brazil, and Rest-of-World

The exposure estimate includes patients who initiated Kalydeco treatment via commercial supply only. The PY estimate is based on initial delivery and re-order supply data using the number of days of treatment supplied for patients initiated during the commercial supply period (varies from country to country) enumerated over all patients. Compliance is calculated based on the number of patients exposed to IVA, comparing the expected number of packs sold to the actual number of packs sold. This compliance calculation is used when estimating the total PY. Days of treatment are counted between the first day of authorisation (e.g., 23 July 2012 in the EU) and 23 January 2024 for the cumulative exposure. Of note, the distribution by age and sex were not available due to privacy restrictions.

United States and Canada

The exposure estimate includes patients who initiated Kalydeco treatment via commercial supply only. The PY estimate is based on initial delivery, and re-orders supply data. US cumulative exposure was estimated from 31 January 2012 to 23 January 2024. Due to HIPAA regulations and providers reporting practices in the US, genotype data are not available.

Canadian cumulative exposure data were estimated from 26 November 2012 through 23 January 2024.

SV.1.2 Exposure

Worldwide cumulative patient exposure to IVA from marketing experience is presented in Table 7. As of 23 January 2024, 8,412 patients were exposed to IVA worldwide since the authorisation for a total of 31,242.4 PY: [redacted] patients in the US, [redacted] patients in the EEA, [redacted] patients in the UK, [redacted] patients in Australia, [redacted] patients in Canada, [redacted] patients in Israel, [redacted] patients in Switzerland, and [redacted] patients in Brazil. Globally, 573 patients received Kalydeco in various managed access programs.

Cumulative patient exposures are provided for the EEA and UK by country in Table 8. Cumulative patient exposures for the US by age and sex are provided in Table 9. Cumulative patient exposure for Canada by age and sex are provided in Table 10. Patient exposures by age, sex, and genotype for Australia, Israel, Switzerland, New Zealand, and Brazil are not available due to privacy protection.

Table 7 Estimated Worldwide Cumulative Patient Exposure to IVA From Marketing Experience

Country[a]	Patients (Estimated)[b]	Person-Years (Estimated)[c]
European Economic Area	[redacted]	
United Kingdom		
United States		
Canada		
Australia		
Switzerland		
Brazil		
Rest of the World[d]	188	427.8

Managed Access Programs[e]	573	832.3
Total	**8,412**	**31,242.4**

IVA: ivacaftor.
Notes:
[a] Methodology for US and Canada has been revised since 23 January 2022 to prevent duplication of patients who change from receiving dispenses from a specialty pharmacy to directly from a hospital during the course of therapy.
[b] Robust data for patient exposure estimates in the for European Economic Area, United Kingdom, Australia, Switzerland, Israel, Brazil and Rest of the World are available only from 2018 through the Data Lock Point of 23 January 2024.
[c] Cumulative person-year estimates for European Economic Area, United Kingdom, Australia, Switzerland, Israel, Brazil and Rest of the World are the sum of cumulative estimates from Kalydeco PSUR13 with Data Lock Point of 23 January 2023 and the PSUR14 1-year reporting interval (24 January 2023 – 23 January 2024).
[d] Rest of the World includes Argentina, Bahrain, Chile, Colombia, Cyprus, Kuwait, Macedonia, New Zealand, Oman, Russian Federation, Saudi Arabia, and UAE.
[e] The Managed Access Program tally does not include 44 patients from the US Expanded Access Program (2010 through 2012), for which exposure was not available.

SV.1.2.1 European Economic Area, Northern Ireland, and Great Britain

Table 8 Estimated Cumulative Patient Exposure to IVA From Marketing Experience in the European Economic Area and United Kingdom by Country

Country	Patients (Estimated)[a]	Person-Years (Estimated)[b]
Austria		
Belgium		
Bulgaria		
Czech Republic		
Denmark		
France		
Germany		
Greece		
Iceland		
Italy		
Malta		
Netherlands		
Norway		
Poland		
Portugal		
Republic of Ireland		
Romania		
Slovakia		
Slovenia		
Spain		
Sweden		
Turkey		
United Kingdom		
England		
Gibraltar		
Northern Ireland		
Scotland		
UK Crown Dependencies		
Wales		
Total	**3,786**	**18,771.8**

IVA: ivacaftor.
[a] Robust data for patient exposure estimates in the for European Economic Area and United Kingdom are available only from 2018 through the Data Lock Point of 23 January 2024.

[b] Cumulative person-year estimates for European Economic Area and United Kingdom are the sum of cumulative estimates from Kalydeco PSUR13 with Data Lock Point of 23 January 2023 and the PSUR14 1-year reporting interval (24 January 2023 – 23 January 2024).

SV.1.2.2 United States and Canada

Table 9 Estimated Cumulative Patient Exposure to IVA From Marketing Experience in The United States by Age and Sex

	[redacted]				Total[a]	
Age	**Patients**	**Person-Years**	**Patients**	**Person-Years**	**Patients**	**Person-Years**
<2 years	[redacted]					
2 to <6 years						
6 to <12 years						
12 to <18 years						
≥18 years						
Unknown						
Total						

IVA: ivacaftor

[a] For 534 patients (1,629.5 person-years), the sex and age were unknown.

Table 10 Estimated Cumulative Patient Exposure to IVA From Marketing Experience in Canada by Age and Sex

	[redacted]				Total[a]	
Age	**Patients**	**Person-Years**	**Patients**	**Person-Years**	**Patients**	**Person-Years**
<2 years	[redacted]					
2 to <6 years						
6 to <12 years						
12 to <18 years						
≥18 years						
Unknown						
Total						

IVA: ivacaftor

[a] For 15 patients (23.7 person-years), the sex and age were unknown.

SV.1.2.3 Exposure in Patients With Relevant Comorbidities

Data of IVA exposure in special populations, including pregnant or lactating women, patients with cardiac disease, patients with moderate or severe hepatic impairment, and patients with ppFEV$_1$ <40 was not collected by the MAH in any region. The exposure of IVA in these populations was estimated based on data from the UK and US patient registries.

As presented in the final report of the LTSS, a post-authorisation safety study (PASS), among 1,858 US CF patients treated with ivacaftor in 2016, 22 (1.2%) patients had hepatic impairment and 160 (8.6%) had ppFEV$_1$ <40. Cardiac disease is rare among patients treated with IVA and is not captured by the registry as a standard variable. Among 484 female patients in US CF Foundation Patient Registry who were 14 years and older and were exposed to IVA in 2016, 28 (5.8%) pregnancies were reported.

In the final LTSS report, analysis of the 2016 UK IVA Cohort showed that among 462 patients, 3 (0.7%) had hepatic impairment, 41 (8.9%) had ppFEV$_1$ <40; and 2 (0.4%) had cardiac disease. There were [redacted] pregnancies reported out of [redacted] female patients in the UK CF Registry who were 14 years and older and were exposed to IVA in 2016.

SVI Additional EU Requirements for Safety Specification

Potential for Misuse for Illegal Purposes

IVA has no known desirable neurologic or psychiatric effects, and no addictive potential. In animal studies, IVA was shown to not cross the blood-brain barrier and the AEs observed in clinical studies do not suggest a potential for abuse.

It is not known whether IVA could be used for manufacturing of illicit drugs; however, given the expected high expense of this drug, the risk of its misuse for such manufacturing is negligible.

IVA is available by prescription only.

SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in this RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised).

The Kalydeco SmPC describes the following adverse reactions that are not considered as important risks because these adverse reactions are mostly mild to moderate in severity, non-serious and did not result in study drug discontinuation, and therefore do not impact the benefit-risk profile.

- Upper respiratory tract infection
- Nasopharyngitis
- Rhinitis
- Headache
- Dizziness
- Ear pain
- Ear discomfort
- Tinnitus
- Tympanic membrane hyperaemia
- Vestibular disorder
- Ear congestion
- Oropharyngeal pain
- Nasal congestion
- Sinus congestion
- Pharyngeal erythema
- Abdominal pain
- Diarrhoea
- Rash
- Breast mass
- Breast inflammation
- Gynaecomastia
- Nipple disorder
- Nipple pain
- Bacteria in sputum

The Kalydeco SmPC describes additional adverse reactions when used in combination with tezacaftor/ivacaftor (nausea) or ivacaftor/tezacaftor/elexacaftor (rhinitis, rhinorrhoea, abnormal breathing, wheezing, blood creatine phosphokinase increased, abdominal pain upper, flatulence, hypoglycaemia, acne, and pruritus) that are not considered as important risks because these adverse reactions are mostly mild to moderate in severity, non-serious, and did not result in study drug discontinuations. Additionally, the ivacaftor/tezacaftor/elexacaftor ADR of increased blood pressure is based on a mild increase from baseline (mean systolic blood pressure increase between 2.0 and 3.5 mm Hg), which is

unlikely to be clinically relevant or have a significant impact on the benefit risk profile in the normotensive CF population. The ivacaftor/tezacaftor/elexacaftor ADR of influenza was reported in IVA clinical studies with a similar incidence between the IVA monotherapy and placebo groups.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no important identified risks for IVA. Descriptions of the important potential risks and missing information at the initial approval are provided herein; changes are captured in Section SVII.2.

SVII.1.2.1 Important Potential Risk – Effect on Liver Function Tests

In the pooled placebo-controlled studies, LFT elevations were well balanced between the placebo and IVA treatment groups across all age subgroups. Looking at both the placebo-controlled and uncontrolled studies, the percentage of subjects with ALT/aspartate aminotransferase (AST) elevations >3 × ULN in the IVA groups was also similar across the paediatric age groups (6 to 11, 12 to 17) and those aged ≥18 years.

Benefit-Risk Impact
Overall, the totality of the LFT data does not suggest an association with IVA, although, IVA's role in contributing to LFT elevations in some patients, such as those with a history of LFT elevations cannot be fully excluded. Therefore, effect on LFTs is considered an important potential risk.

SVII.1.2.2 Important Potential Risk - Cataracts

The juvenile rat toxicity study performed to support dosing of ivacaftor in subjects <2 years of age demonstrated the presence of lens opacities among juvenile rats when dosed with IVA beginning at PND 7 though PND 35, particularly at the highest dose tested (50 mg/kg/day). Based on available information, however, the relevance of the finding to humans is not clear.

Benefit-Risk Impact
Given the findings in the juvenile rat toxicity study, comprehensive ophthalmologic examinations were performed in clinical studies for subjects aged 11 years and younger. Although there is a high background rate of cataracts in CF patients, as evidenced through literature reports and large Phase 3 baseline screening examinations, as well as potentially confounding factors (such as chronic steroid use in the CF population and family history), available evidence does not suggest an association between IVA treatment and cataract development or progression, a contributing role cannot be completely excluded. Therefore, cataracts are considered an important potential risk.

SVII.1.2.3 Important Potential Risk – Concomitant Use of Ivacaftor With Strong CYP3A Inhibitors or Inducers

As a substrate of CYP3A, IVA metabolism may be impacted by concomitant use with a potent CYP3A inhibitor or inducer.

Benefit-Risk Impact
Changes in the metabolism of IVA may result in over-exposure or loss of efficacy. Therefore, concomitant use of IVA with strong CYP3A inhibitors or inducers is considered an important potential risk.

SVII.1.2.4 Important Potential Risk – Cardiac Arrhythmias

In vitro studies showed that IVA inhibited the hERG channel, although at a much higher IVA concentration than needed for CFTR potentiation (>2000-fold window). In the 12-month chronic toxicity study in dogs, there was a slight increase in the incidence of SVPC runs, consisting of multiple events within a single ECG recording, at dosages ≥30 mg/kg/day. The SVPCs were not associated with biochemical or morphological changes in the heart or changes in health status of the 3 dogs affected. The SVPCs resolved following the 1-month recovery period. Whilst the finding was not considered to be adverse, there appeared to be a possible dose-related association with IVA.

Benefit-Risk Impact
The SVPC findings in the toxicity study in dogs led to the implementation of 24-hour ambulatory ECG monitoring in the placebo-controlled Phase 2B/3 studies in human. Overall, treatment with IVA did not demonstrate an increased incidence of clinically significant cardiac arrhythmias, including supraventricular ectopy, or any other cardiac findings, demonstrated through intense monitoring (12-lead and 24-hour ambulatory ECGs). Given the limitations of detecting these events in the context of the clinical studies, cardiac arrhythmias is considered an important potential risk.

SVII.1.2.5 Important Potential Risk – Off-label Use in Children Less Than 6 Years of Age and in Patients With Other Mutations (Non-G551D-CFTR Gating Mutations and Non-Class III Mutations)

The efficacy, safety, and PK of IVA have not been evaluated in subjects with CF less than 6 years of age or subjects without the *G551D* mutation. Because clinical features of CF can manifest in the first few years of life, it is possible that early interventions may impact disease progression. Furthermore, in vitro data show that IVA enhances channel gating and chloride transport in a variety of defective CFTR proteins, if present on the epithelial surface. The mechanism of action of IVA therefore suggests that patients with other *CFTR* mutations might also benefit from IVA treatment.

Benefit-Risk Impact
The effect of IVA in children less than 6 years of age and in subjects with *CFTR* mutations besides *G551D* are not expected to differ, based on available Phase 2b/3 data from Studies 102, 103, and 104. Given the lack of benefit in patients with CF with mutations that do not have residual CFTR activity at the epithelial cell surface (i.e., subjects homozygous for the *F508del-CFTR* in Study 104), use in patients not indicated is considered an important potential risk.

SVII.1.2.6 Missing Information – Use in Pregnant and Lactating Women

Benefit-Risk Impact
As a standard precautionary measure, pregnant and lactating women were excluded from clinical studies. In the post-authorisation use, it may be expected that there will be pregnant women treated with IVA. In nonclinical studies, IVA was not teratogenic when orally dosed to pregnant rats and rabbits during the organogenesis stage of foetal development at doses approximately 5 times (for IVA and metabolites) and 11 times (on an IVA AUC basis) the MRHD. IVA impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (yielding exposures approximately 8 and 5 times, respectively, the summed AUCs of ivacaftor and its major metabolites at the human therapeutic dose) when females were dosed prior to and during early pregnancy.

^{14}C-labelled IVA accumulated in the milk of pregnant and lactating rats. It is unknown whether IVA and/or its metabolites are excreted in human milk. The safe use of Kalydeco during breastfeeding has not been established.

Any information that would help further reassure this assumption is of particular value. Therefore, safety in pregnant and lactating women is considered to be missing information.

SVII.1.2.7 Missing Information – Pulmonary Exacerbations and Bacterial Sputum Colonisation with Long-term Ivacaftor Treatment

Benefit-Risk Impact
AE data from the Phase 3 Studies 102 and 103 showed that bacteria in sputum occurred in 7.3% of subjects in the IVA group compared to 3.8% of subjects in the placebo group. Because bacterial colonisation is closely monitored in patients with CF and colonisation with particular organisms is associated with a more rapid decline in lung function, pulmonary exacerbations and bacterial sputum colonisation are considered to be missing information.

SVII.1.2.8 Missing Information – Use in Children Between 6 and 11 Years Old

Benefit-Risk Impact
The IVA clinical development programme evaluated the safety, PK, and efficacy of IVA in a limited number of subjects between 6 and 11 years of age. Whilst the safety profile in these subjects was not substantively different from that in the older subjects, further characterisation in the post-marketing setting is needed. Use in children between 6 and 11 years of age is considered missing information.

SVII.1.2.9 Missing Information – Patients with FEV_1 <40%

Benefit-Risk Impact
Whilst the mechanism of action for ivacaftor is independent of the level of lung function, limited data are available in patients with $ppFEV_1$ <40. Because the indication includes patients with any level of lung function, use in patients with $ppFEV_1$ <40 is considered to be missing information.

SVII.1.2.10 Missing Information – Safety in Patients With Cardiac Disease

Benefit-Risk Impact
No studies were performed to evaluate the safety of IVA in patients with cardiac diseases. Patients with CF are not known to have any increased incidence or prevalence of intrinsic cardiac disease. Any such cardiac symptomatology is usually secondary to other CF pathophysiology, particularly pulmonary disease. Whilst IVA demonstrated no effect on the QT interval in a well-controlled ECG study and did not have the potential to cause ECG abnormalities, further characterisation in the post-marketing setting is needed. Safety in patients with cardiac disease is considered missing information.

SVII.1.2.11 Missing Information – Long-term Safety

Benefit-Risk Impact
The longest clinical study experience with IVA treatment in clinical studies is 216 weeks. As a chronic treatment, further characterisation of the long-term safety of IVA in the post-marketing setting is needed.

SVII.1.2.12 Missing Information – Clinical Relevance of P-gp Inhibition by Ivacaftor

Benefit-Risk Impact
In vitro studies showed that IVA and metabolite M6 are not substrates for P-gp transporters, whilst metabolite M1 is a substrate for P-gp. Based on in vitro data, IVA and M1 (but not

M6) inhibit P-gp. For P-gp substrates with a narrow therapeutic index, such as digoxin, use with caution and appropriate monitoring is recommended. Clinical significance of the P-gp inhibition is identified as important missing information.

SVII.1.2.13 Missing Information – Patients With Moderate or Severe Hepatic Impairment

Benefit-Risk Impact
There is limited information in patients with Child-Pugh Class B and studies have not been conducted in subjects with severe hepatic impairment (Child-Pugh Class C). Therefore, further characterisation in the post-marketing setting is needed. Safety in patients with moderate or severe hepatic impairment is considered missing information.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

SVII.2.1.1 Updated Important Potential Risk – Hepatotoxicity

The important potential risk of "effects on LFTs" was updated to "hepatotoxicity" as per recommendations from PRAC and CHMP in EU RMP Version 4.9.

SVII.2.1.2 Removed Important Potential Risk – Off-label Use in Children and Adolescents Not of an Approved Age and in Patients Without an Approved CFTR Mutation

The important potential risk for off-label use was revised in EU RMP Version 2.8 and Version 4.9 to reference the non-indicated population (i.e., "not of an approved age" and "without an approved *CFTR* mutation") instead of specific age groups and *CFTR* mutations. Since the initial marketing authorisation, the approved indication of IVA was expanded to include patients of younger age (i.e., aged 2 years and older), and other *CFTR* mutations including non-*G551D* gating (Class III) and the *R117H* mutation; a clinical study with ivacaftor in patients <2 years of age is currently ongoing. Subsequently, IVA in combination with LUM (Orkambi®) was approved for patients aged 6 years and older with 2 copies of the *F508del* mutation, which accounts for approximately 50% of the CF population. With these additional approved populations for IVA and the approved treatment of lumacaftor/ivacaftor, the potential for off-label use with IVA was reduced significantly.

In addition to the reduced potential (available population) for off-label use, the safety profile of IVA has been demonstrated to be similar across age groups and *CFTR* genotype. Therefore, no specific risk is anticipated with off-label use in those patients with an unapproved age or indication. As such, this missing information was removed during the 5-year renewal procedure for Kalydeco.

SVII.2.1.3 Removed Missing Information – Pulmonary Exacerbation and Bacterial Sputum Colonisation With Long-term Ivacaftor Treatment

The missing information of "pulmonary exacerbation and bacterial sputum colonisation with long-term IVA treatment" was removed in EU RMP Version 5.7 as part of the 5-year renewal procedure for Kalydeco. The clinical efficacy and safety data demonstrate substantial reduction in CF pulmonary exacerbations in comparison to placebo, which was maintained through 144 weeks of IVA treatment. The results were confirmed across the annual interim analyses from the LTSS, which demonstrated a consistent favorable effect of IVA treatment in reducing pulmonary exacerbations, bacteria colonisation and slowing CF disease progression. In addition, publications across multiple effectiveness reports of clinical

experience also demonstrate a reduction in pulmonary exacerbations as well as significant improvements in measures of lung disease.

The cumulative evidence provided no basis to suggest an association between IVA treatment and increased risk bacterial colonisation or pulmonary exacerbations and did not support the maintenance of "pulmonary exacerbation and bacterial sputum colonisation with long-term IVA treatment" as missing information in the RMP.

SVII.2.1.4 Updated Missing Information – Indicated Use in Children Aged Less than 6 Years

The age range in the missing information of use in children was updated to include indicated ages and to revise the upper limit to those less than 6 years. Based on changes in the lower end of the indicated age and the limited study size supporting these changes, the missing information was expanded to include children aged 2 to 5 years (in procedure /0034/G), children aged 12 to <24 months (in procedure /0069), and children aged 6 to <12 months (in procedure /0075). Furthermore, ongoing studies (in the pharmacovigilance plan and the post-authorisation efficacy study [PAES]) are evaluating children aged less than 6 years; therefore, the missing information was reformulated as "less than 6 years".

SVII.2.1.5 Removed Missing Information – Patients With FEV_1 <40%

The missing information of "patients with FEV_1 <40%" was removed in EU RMP Version 5.7 from the 5-year renewal procedure for Kalydeco. Overall, the cumulative data from clinical studies, compassionate use programs, the LTSS, published literature, and post-marketing experience in subjects and patients with FEV_1 <40% demonstrated that IVA treatment in patients with FEV_1 <40% resulted in clinical meaningful and durable treatment benefit, comparable to patients with FEV_1 ≥40%, without any specific safety concerns.

SVII.2.1.6 Removed Missing Information – Clinical Relevance of P-gp Inhibition

The missing information of "clinical relevance of P-gp inhibition" was removed in EU RMP Version 5.7 from the 5-year renewal procedure for Kalydeco. In vitro studies showed that IVA and metabolite M6 are not substrates for P-gp transporters, whilst metabolite M1 is a substrate for P-gp. In vitro data also indicated that IVA and M1 (but not M6) are inhibitors of P-gp.

Because of in vitro data showing ivacaftor and metabolite M1 as inhibitors of P-gp and M1 as a substrate of P-gp, a DDI study was conducted with digoxin, a sensitive P-gp substrate (Study 016). The results showed a 32% increase in digoxin AUC when a single dose of digoxin was co administered with IVA at steady-state, indicating weak inhibition of P-gp. For substrates of CYP3A and/or P-gp with a narrow therapeutic index such as digoxin, cyclosporine, or tacrolimus, use with caution and appropriate monitoring is recommended.

Overall, the clinical study and post-marketing experience has demonstrated limited use of digoxin in IVA-treated patients, without reports of acute or chronic digoxin toxicity. Given the weak inhibition nature of IVA on P-gp, the missing information was removed from the RMP.

SVII.2.1.7 Removed Missing Information – Long-term Safety

The long-term safety was evaluated in a number of open-label extension studies (e.g., Studies 105, 109, and 112) and in the LTSS (ANX 001.5). Results from long-term extension studies showed consistent safety data as compared to the pivotal studies, without new safety concerns with extended IVA treatment. The results of annual analyses in the LTSS of real-world observational data from 2 large, independent CF patient registries from the first year of

commercial availability of IVA (2012 in the US and 2013 in the UK) through 2016 indicated no new safety concerns and in fact demonstrated consistently lower risks of key clinical outcomes and delayed disease progression with IVA treatment. These findings are consistent with the current understanding of the IVA benefit-risk profile and support disease modification by CFTR modulation with IVA treatment.

The LTSS results are generalizable to the approved indications in the CF population worldwide because the majority (over 80%) of CF patients in the US are part of the CF Foundation Patient Registry, and all patients in the UK are enrolled in the CF Registry (the UK patients represent approximately 25% of the CF patients in the EU).[66,67]

Furthermore, these results reflect the growing body of literature supporting disease modification by CFTR modulation.[65,68-73] The results are consistent with findings of long-term IVA treatment in clinical studies and with other published observational studies outlining similar outcomes among IVA-treated subjects. For example, in the GOAL (*G551D*, observational) study evaluating 133 patients with CF across 28 US centers, the proportion of subjects who were hospitalised during the 6 months following IVA initiation declined by 19.1% compared with either the 6 months immediately before IVA or with the same 6-month span in the year before IVA use.[71] Significant improvements in hospitalisation rates and pulmonary exacerbations were also observed at the 1-year follow-up.[70] In addition, in a small study of 10 subjects at a single center, IVA also appeared to reduce hospitalisations 1 year post initiation.[69]

In summary, the data in the LTSS are robust, achieving statistical significance for many endpoints that are consistent across time, across registries in different regions, and with the published literature. These results provide important and highly relevant clinical data that provide valuable guidance to clinicians regarding the favourable benefit/risk profile and outcomes of long-term IVA treatment in a real-world setting. The high rate of premature mortality, extensive pulmonary morbidity, and progressive organ failure requiring transplantation comprise the natural history of CF; these data demonstrate the beneficial impact of IVA therapy on key outcomes and disease progression. Therefore, "long-term safety" is no longer considered as missing information, although the safety of IVA use will continue to be monitored through routine pharmacovigilance activities.

SVII.2.1.8 Removed Important Potential Risk – Cardiac Arrhythmias

The important potential risk of "Cardiac arrhythmias" was removed as part of procedure /0075, as requested by PRAC. Searches of the global safety database using the standardized MedDRA query of Cardiac arrhythmias identified a limited number of cases (and fewer serious cases), which do not suggest an association between IVA and cardiac arrhythmias. Furthermore, long-term, open-label Study 109 and Study 112 did not reveal any cardiac concerns. Overall, the clinical study and post-marketing experience have demonstrated that "cardiac arrhythmias" is not an important potential risk; however, any cardiac event will continue to be monitored through routine pharmacovigilance activities.

SVII.2.1.9 Removed Missing Information – Safety in Patients with Cardiac Disease

The missing information of "Safety in patients with cardiac disease" was removed as part of procedure /0075, as requested by PRAC. Searches of the global safety database for patients with a comorbidity of the MedDRA system organ class (SOC) of Cardiac disorders identified relatively few patients, most with few or no cardiac AEs. The AEs reported from these cases were mostly common CF manifestations. Overall, the reports in patients with a significant relevant medical history of cardiac disease did not suggest a significant difference in the

types of events while on IVA treatment, and no patterns, trends, or specific risks have been demonstrated in this patient group.

SVII.2.1.10 Removed Missing Information – Safety in Patients with Moderate or Severe Hepatic Impairment

The missing information of "Safety in patients with moderate or severe hepatic impairment" was removed as part of procedure /0075, as requested by PRAC. Searches of the global safety database for patients with a comorbidity of the MedDRA SOC of Hepatobiliary disorders identified relatively few patients in the post-marketing setting, and their hepatic impairment status was not always indicated by the reporter. Given that "Hepatotoxicity" is already addressed as an important potential risk, the evaluation of safety in patients with hepatic impairment has not revealed any new safety concern and is removed from the RMP.

SVII.2.1.11 Removed Important Potential Risk – Concomitant Use of IVA with Strong CYP3A Inhibitors or Inducers

The important potential risk of "Concomitant use of IVA with strong CYP3A inhibitors or inducers" was removed as part of procedures /0089 and /0094, as recommended by PRAC in procedure/0075. There are no additional pharmacovigilance or risk minimisation activities associated with this potential risk. Searches of the global safety database for patients with a comorbidity of the MedDRA high level term (HLT) of Interactions identified relatively few patients in the postmarketing setting and the majority of cases involved drugs interactions already noted in the SmPC. Review of cases with reported use of known strong CYP3A inhibitors or inducers also did not identify any patterns, trends, or specific risks associated with potential drug interaction.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Potential Risk - Hepatotoxicity

Potential mechanisms
IVA is metabolised by the liver. However, comorbidities such as infections, pyrexia, and CF pulmonary exacerbations, as well as concomitant medication use may have also contributed to the increased liver enzyme tests. Furthermore, underlying CF-related liver diseases may have been developing and/or progressing in some individuals during the 48-week Phase 3 studies.

Exploratory analyses aimed to evaluate the relationship between exposure to IVA or its major metabolites (M1 and M6) and transaminase elevations were conducted in subjects with marked (>5 × upper limit of normal [ULN]) transaminase elevations (ALT, AST). Results showed no apparent relationship between increased exposure to ivacaftor or its major metabolites and elevated transaminases.

Evidence source(s) and strength of evidence
Elevated liver enzymes were reported during Phase 2b/3 studies with IVA; however, elevations in transaminases are common in patients with CF. A contributing role of IVA is uncertain but cannot be excluded.

Characterisation of the risk
In the pooled placebo-controlled studies, the LFT elevations were well balanced between the placebo and IVA treatment groups across all age subgroups. Looking at both the placebo-controlled and uncontrolled studies, the percentage of subjects with ALT/AST

elevations >3 × ULN in the IVA groups was also similar across the paediatric age groups (6 to 11, 12 to 17) and those aged ≥18 years. However, transaminase elevations >3 × ULN were more common in the 2- to 5-year-old group. An analysis of the maximum on-treatment ALT and AST elevations by age subgroup and pre-treatment values in placebo-controlled and uncontrolled studies showed that, in Studies 108 and 109, the majority of elevations occurred in subjects with pre-treatment ALT or AST elevations >2 × ULN. In the other clinical studies of IVA, this trend is less evident, most likely due to the lower prevalence and magnitude of pre-treatment elevations in the older subject population.

The difference in the transaminase elevations seen in the 2- to 5-year olds and the ≥6 years is not totally unexpected given the higher prevalence and magnitude of pre-treatment LFT elevations in Study 108 as compared to the previous studies in older subjects. Despite the magnitude of the elevations in Studies 108 and 109, none of the subjects had concurrent ALT/AST elevations >3 × ULN and total bilirubin >2 ×ULN; no additional evidence of liver damage (e.g., AEs, imaging findings) was seen; nearly all subjects had alternative etiologies for the elevations; and most subjects did not have further significant elevations with continued ivacaftor treatment. Across Studies 108 and 109, analysis by 24-week treatment interval demonstrated each interval was similar, and no trend of increasing incidence or severity of transaminase elevations was noted with prolonged ivacaftor treatment for up to 108 weeks. Nevertheless, the SmPC language recommends more frequent monitoring of LFTs for patients with a history of transaminase elevations.

In subjects aged 4 to <24 months at the initiation of IVA in Study 124, mean changes from baseline in LFTs were variable throughout the 24-week treatment period and were not considered clinically significant. The majority of subjects had maximum on-treatment ALT or AST ≤2 × ULN. Six subjects had transaminase elevations (ALT) >3 × ULN (5 subjects aged 12 to <24 months and only 1 subject aged 6 to <12 months). Four subjects had ALT >3 to ≤5 × ULN (3 subjects aged 12 to <24 months and 1 subject aged 6 to <12 months) and remained on study drug continuously. Two subjects (aged 12 to <24 months) had ALT >8 × ULN; both had alternative etiologies (concurrent infections) and resumed treatment following a short period of study drug interruption with no further elevations. No subjects had total bilirubin levels above the normal range.

Treatment-emergent LFT-related AEs, serious adverse events (SAEs), and AEs leading to study drug discontinuation were analyzed across placebo-controlled and uncontrolled studies. Overall, the incidence of LFT-related AEs was well-balanced between the placebo and IVA treatment groups in the controlled studies. Similar to the laboratory transaminase elevations, AEs related to transaminase elevations also appeared to be more common in subjects younger than 6 years of age. However, the nature and severity of these events were similar to those in subjects aged ≥6 years, i.e., mostly presenting as asymptomatic, isolated transaminase elevations, without concurrent bilirubin elevations.

Kaplan-Meier analyses for the time-to-first ALT and AST elevations >3 × ULN in Studies 102, 103, 105, 108, 110, and 111 did not demonstrate any discernible pattern supporting a difference between the placebo and ivacaftor groups or between the controlled and uncontrolled studies.

Overall, the totality of the LFT data does not suggest an association with IVA; however, its role in contributing to LFT elevations in some patients, such as those with a history of LFT elevations, cannot be fully excluded.

In post-authorisation data to date, the number of subjects with ALT and/or AST elevations >5 × ULN was low. The nature and severity of post-marketing reports related to transaminase elevation were consistent with those observed in the clinical studies.

Risk factors and risk groups
Only generally known risk factors for increases in liver enzymes were identified in several instances, including concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, haemoptysis, kidney infection), as well as concomitant drugs (e.g., acetaminophen, antibiotics) and substances (e.g., alcohol) known to be associated with liver enzyme elevations.

Preventability
No preventative measures have been identified. Drug withdrawal (de-challenge) is the general standard measure in cases of elevated transaminases that might indicate drug-induced liver injury to prevent worsening and potentially reverse liver damage.

Impact on the benefit-risk balance of the product
Elevations of transaminases were observed with IVA. In clinical studies, the incidence and clinical features of these elevations was similar between subjects in the IVA and placebo groups. In subjects aged 2 to <6 years, the incidence of marked transaminase elevations was more common than that observed in subjects of older age. However, risk factors were present in nearly all cases. In subjects aged <24 months, fluctuations from baseline were not considered clinically significant. Most patients with marked transaminase elevations continued or successfully resumed IVA treatment without further elevations. The majority of post-marketing reports have been consistent with the safety profile established in the clinical studies.

Overall, the role of IVA in contributing to transaminase elevations is uncertain. Nevertheless, the potential effect of IVA on LFTs and hepatotoxicity is described in the prescribing information. Further characterisation via the pharmacovigilance plan and the routine risk minimisation measures will be conducted to assess the appropriateness of the measure in place.

Public health impact

Given that the effects on liver function were generally reversible without long-term sequelae and the uncertainty of a causal association with IVA, no significant impact on public health is expected.

SVII.3.1.2 Important Potential Risk - Cataract

Potential mechanisms

Although the etiology of the cataracts in rats is unknown, it is likely that it is related to factors specific to the development of lens tissues in the eye of albino rats. One hypothesis to explain the observation of IVA-induced cataracts in juvenile rats, with no evidence of cataracts after chronic dosing in adult rats, relates to factors unique to the developing lens in newborn albino rats and, in particular, the developing vasculature, namely the hyaloid vessels.

Evidence source(s) and strength of evidence
Lens opacities (cataracts) were observed in newborn rats and were considered IVA related. This finding has not been observed in older animals. Given species developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 6 years of age and older. Non-congenital cataracts have been reported, although risk factors

(e.g., corticosteroid use) were present, a contributing role of IVA cannot be completely excluded.

Characterisation of the risk
In clinical studies of up to 2 years in duration (exposure to IVA for up to 3 years), 3 out of 111 subjects had cataracts, with no treatment-emergent cataracts identified in the youngest group evaluated (62 subjects aged 1 to 23 months in Study 124). In the postmarketing ocular Study 115, 11 out of 95 subjects had non-congenital cataracts. In the postmarketing experience of almost 7,000 patients exposed to IVA for >20,000 patient years, 34 post-market reports of lens abnormalities have been received. Overall, 7 reports were considered serious, however with no impact on vision, and thus, not of clinical significance. Reported lens abnormalities will be followed to assess progression while on IVA. To date, 4 reports (2 of which were considered serious) of non-congenital cataract were noted to have resolved in follow-up examinations.

Overall, the reported events were subtle, and generally without impact on vision. Ten of the reports were considered congenital in nature and not progressive. The remaining reports were considered noncongenital. The relationship of cataracts to IVA is uncertain due to 1) lack of baseline ophthalmological examinations, 2) the high prevalence of background lens opacities, 3) the subtlety of the ophthalmological findings, 4) other confounding risk factors, or 5) lack of sufficient information for a meaningful assessment.

Risk factors and risk groups
Risk factors for cataracts include aging, trauma, ultraviolet light and radiation exposure, diabetes mellitus, intraocular inflammation, and systemic or topical corticosteroid use.[68]

Preventability
The preventability of cataracts is unknown; however, early detection is expected to be treatable with surgery.

Impact on the benefit-risk balance of the product
Most of the cases of cataracts with IVA monotherapy are characterised as subtle findings, variable in location, and without impact on vision. Additionally, final data from ocular safety Study 115 and results of Study 109 showed a lack of cataract progression in patients treated with IVA monotherapy based on the Lens Opacity Classification System, Version III (LOCS III) grading.

When coupled with the high background prevalence of lens opacities in CF patients, the subtlety of the ophthalmological findings with no impact on visual acuity, and, most importantly, lack of progression based on the sensitive and more objective LOCS III grading, the non-congenital lens abnormalities identified during the interval may represent background findings rather than suggest an association with IVA.

Overall, the ocular safety data from IVA monotherapy development programmes do not suggest an association between IVA treatment and cataract development or progression, although a contributing role cannot be completely excluded. The potential effect of IVA on cataract is described in study documents and the prescribing information and is monitored to assess the appropriateness of the current pharmacovigilance plan and risk minimisation measures.

Public health impact
No public health impact is expected.

SVII.3.1.3 Missing Information – Use in Pregnant and Lactating Women

Evidence source
Cumulatively since the DIBD, a total of 305 maternal pregnancy exposures to IVA have been reported with outcomes: [redacted]. Of the cases where the action taken was reported, 109 patients continued IVA treatment without change during pregnancy, 43 interrupted IVA treatment, 42 withdrew IVA treatment, and 3 decreased the IVA dose; the action taken was unknown for 105 patients and not applicable for 3. There was no discernible difference in fetal outcomes between those patients who continued IVA in comparison to those who discontinued.

Cumulatively, there were a total of 16 case reports of IVA exposure via father, of which 15 originated from post-marketing sources [redacted]. In 9 of the 16 case reports, the fathers continued IVA treatment without change. [redacted].

Cumulatively, a total of 29 case reports of IVA exposure during breast feeding have been reported. All cases originated from post-marketing sources [redacted]. The reported action taken was no change in 17 cases, unknown in 8, not applicable in 2, and withdrawn in 2.

Overall, no new concerns have arisen from these reports.

Population in need of further characterisation
There is limited experience of IVA use in pregnant or lactating women. Use in pregnant and lactating women will be further characterised in the post-marketing setting.

SVII.3.1.4 Missing Information – Indicated Use in Children Aged Less Than 6 Years

Evidence source
A limited number of paediatric subjects have been evaluated in the clinical development programme. Post-marketing experience indicates that the most common AEs were expected adverse drug reactions or common comorbidities with CF.

Anticipated risk/consequences of the missing information
Overall, the safety profile observed in clinical studies with subjects aged less than 6 years is generally consistent with the overall older subjects treated with IVA. No trends, patterns, or age-specific safety concerns were observed.

SVIII Summary of Safety Concerns

Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

PART III Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Pregnancy Safety Information Collection Form

III.2 Additional Pharmacovigilance Activities

Not applicable

III.3 Summary Table of Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
None				

MA: market authorisation; PD: pharmacodynamics; PV: pharmacovigilance

PART IV Plans for Post-authorisation Efficacy Studies

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the MA				
None				
Efficacy studies which are Specific Obligations in the context of a conditional MA or a MA under exceptional circumstances				
None				

PART V Risk Minimisation Measures

V.1 Routine Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Activities
Hepatotoxicity	**Routine risk communication:** SmPc Sections 4.4 and 4.8 PL Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measure to address the risk: Recommendations for LFT monitoring are included in SmPC Section 4.4 and in PL Section 2
	Other routine risk minimisation measures beyond the Product Information: Prescription only
Cataract	**Routine risk communication:** SmPc Sections 4.4 and 5.3 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: Recommendations for ophthalmologic examinations are included in SmPC Section 4.4 and in PL Section 2.
	Other routine risk minimisation measures beyond the Product Information: Prescription only

Safety Concern	Routine Risk Minimisation Activities
Use in pregnant and lactating women	**Routine risk communication:** SmPc Section 4.6 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: Advice for use during pregnancy or during breastfeeding is included in SmPC Section 4.6.
	Other routine risk minimisation measures beyond the Product Information: Prescription only
Indicated use in children aged less than 6 years	**Routine risk communication:** SmPc Sections 4.8 and 5.2 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: The Kalydeco posology is included in SmPC Section 4.2.
	Other routine risk minimisation measures beyond the Product Information: Prescription only

PL: Patient Leaflet; SmPC: Summary of Product Characteristics

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in PartV.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** None
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** None
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up form **Additional PV activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 Prescription only **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** None

PL: Patient Leaflet; SmPC: Summary of Product Characteristics

PART VI Summary of the RMP

Summary of Risk Management Plan for KALYDECO (ivacaftor)

This is a summary of the risk management plan (RMP) for KALYDECO. The RMP details important risks of KALYDECO, how these risks can be minimised, and how more information will be obtained about KALYDECO's risks and uncertainties (missing information).

KALYDECO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KALYDECO should be used.

This summary of the RMP for KALYDECO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of KALYDECO's RMP.

I. The medicine and what it is used for

KALYDECO tablets are authorised for the treatment of patients with cystic fibrosis (CF) in patients aged 6 years and older and weighing 25 kg or more who have an *R117H-CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. KALYDECO tablets are also indicated in combination regimens:

- with tezacaftor/ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*; and
- with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene.

KALYDECO granules are indicated for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H-CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R* (see SmPC for the full indication). KALYDECO granules are also indicated in combination regimens:

- with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of patients with CF aged 2 years to less than 6 years who have at least one *F508del* mutation in the *CFTR* gene.

KALYDECO contains ivacaftor (IVA) as the active substance and is given orally.

Further information about the evaluation of KALYDECO's benefits can be found in KALYDECO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/kalydeco.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of KALYDECO, together with measures to minimise such risks and the proposed studies for learning more about KALYDECO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of KALYDECO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of KALYDECO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of KALYDECO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

II.B Summary of important risks

Hepatotoxicity	
Evidence for linking the risk to the medicine	Elevated liver enzymes were reported during Phase 2b/3 studies with IVA; however, elevations in transaminases are common in patients with CF. The contributing role of IVA is uncertain but cannot be excluded.
Risk factors and risk groups	Only generally known risk factors for increases in liver enzymes were identified in several instances, including concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, haemoptysis, kidney infection), as well as concomitant drugs (e.g., acetaminophen, antibiotics) and substances (e.g., alcohol) known to be associated with liver enzyme elevations.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 where advice is given on monitoring liver function tests. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Cataract	
Evidence for linking the risk to the medicine	Lens opacities (cataracts) were observed in newborn rats and were considered IVA related. This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown, but given species developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 6 years of age and older. Non-congenital cataracts have been reported, although risk factors (e.g., corticosteroid use) were present, a contributing role of IVA cannot be completely excluded.
Risk factors and risk groups	Risk factors for cataracts include aging, trauma, ultraviolet light and radiation exposure, diabetes mellitus, intraocular inflammation, and systemic or topical corticosteroid use.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Use in pregnant and lactating women	
Risk minimisation measures	SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 Prescription only
Additional pharmacovigilance activities	None
Indicated use in children aged less than 6 years	
Risk minimisation measures	SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 Prescription only
Additional pharmacovigilance activities	None

CF: cystic fibrosis; IVA: ivacaftor; PL: patient leaflet; SmPC: Summary of Product Characteristics

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

PART VII Annexes to the Risk Management Plan

Annex 4 Specific adverse event follow-up forms

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Annex 4 Specific adverse event follow-up forms

- Please complete form and appendices (as applicable) in accordance with local laws and regulations (e.g., personal data protection).
- Completed forms are sent to Vertex Patient Safety via Email: [redacted]

Vertex Global Patient Safety Trikafta (Elexacaftor/Tezacaftor/Ivacaftor and Ivacaftor)	
To:	
Site Contact:	Fax: ; Email:
Date:	
Re:	Patient: ; Manufacturer Control Number:
Reported Event(s):	

Patient Name/Initials *(recipient of drug)*: DOB:	☐Female ☐Male Partner	**Maternal:** Age	Height cm / in	Weight kg / lb
Vertex Drug(s)	**Start Date**	**End Date**	**Dose, Frequency, Route**	
		☐Ongoing		
		☐Ongoing		
Pregnancy Outcome ☐Ongoing ☐Live Delivery ☐Spontaneous Abortion ☐Therapeutic Abortion ☐Elective Termination ☐Stillbirth ☐Unknown				
Infant Information ☐Female ☐Male	Date of Birth:	**APGAR** 1 min: 5 min:	Height cm / in	Weight kg / lb
Narrative *(Pregnancy details, gestational week, LMP, estimated date of conception, estimated due date; Birth outcome: normal / abnormal).*				
Relevant Maternal History / Risk Factors *(e.g., comorbidities, genetic disorders, reproductive complications, alcohol or drug use)*				

Relevant Concomitant Medications	**Indication**	**Start Date**	**End Date**	**Dose, Frequency, Route**

Report Completed By (Name/Title):	Institution/Country:	**Reporter Signature / Date:**
Email:	Fax: Phone:	
If unable to provide information requested above, please provide additional contact information (e.g., OBGYN, Pediatrician):		

Information for Adverse Events Associated With Pregnancy

Adverse Event *(if associated with pregnancy*)*:			**Start Date**	**End Date**
Seriousness Criteria *(if applicable)* ☐ Hospitalization Date of Admission: Discharge: ☐ Important Medical Event ☐ Life-threatening ☐ Permanent Disability ☐ Congenital Anomaly ☐ Death Date of Death:			**Event Outcome** ☐ Recovered / Resolved ☐ Recovering / Resolving ☐ Recovered / Resolved w Sequelae ☐ Not Recovered / Not Resolved (Ongoing) ☐ Fatal ☐ Unknown	
Vertex Drug(s)	**Related**	**Not Related**	**1**- Interrupted, **2**- Withdrawn, **3**- Not changed, **4**- Reduced, **5**- Not Applicable	
	☐	☐		
	☐	☐		
Alternative suspected etiology(ies):				
Narrative				

**For all other reportable adverse events, please report to Vertex Global Patient Safety using the standard reporting form in accordance with standard procedures.*

Infant Follow-up Information

INFANT FOLLOW-UP ☐ **6-MONTHS** ☐ **12-MONTHS**			
Date of Birth (*dd-mmm-yyyy):*	Status: ☐Normal ☐Abnormal	Height cm / in	Weight kg / lb
Has an ophthalmologic examination been performed? Yes ___ No ___ **If yes, please provide date of exam and any relevant findings:**			
Adverse Event *(if any birth defects*):*		**Start Date**	**End Date**
Seriousness Criteria *(if applicable)* ☐ Hospitalization Date of Admission: Discharge: ☐ Important Medical Event ☐ Life-threatening ☐ Permanent Disability ☐ Congenital Anomaly ☐ Death Date of Death:		**Event Outcome** ☐ Recovered / Resolved ☐ Recovering / Resolving ☐ Recovered / Resolved w Sequelae ☐ Not Recovered / Not Resolved (Ongoing) ☐ Fatal ☐ Unknown	

Vertex Drug(s)	**Related**	**Not Related**	**1-** Interrupted, **2-** Withdrawn, **3-** Not changed, **4-** Reduced, **5-** Not Applicable
	☐	☐	
	☐	☐	

Alternative suspected etiology(ies):
Narrative

**For all other reportable adverse events, please report to Vertex Global Patient Safety using the standard reporting form in accordance with standard procedures.*

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

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