# Module 1.8.2

# EU RISK MANAGEMENT PLAN (EU-RMP)

For ORKAMBI (lumacaftor/ivacaftor)

**RMP Version Number:** 11.5
**Data lock for this RMP:** 01 February 2024
**Date of final sign off:** 05 February 2024

**Rationale for submitting an updated RMP:** This RMP was updated to reflect the completion of Study 124 (open-label rollover study from Study 122).

**Summary of significant changes in this RMP:** The RMP was updated to

- reflect the completion of Study 124;
- indicate that the post-authorisation efficacy study (PAES) was expanded to evaluate patients who initiated Orkambi at 1 to less than 2 years of age; and
- include the updated post-market pregnancy safety information collection form in Annex 4.

## 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 |
|---|---|---|
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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 |
|---|---|
| AE | adverse event |
| AESI | adverse event(s) of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATP | adenosine 5'-triphosphate |
| ATU | Autorisation Temporaire d'Utilisation (France) |
| AUC | area under the concentration versus time curve |
| AV | atrioventricular |
| BCRP | breast cancer resistance protein |
| BP | blood pressure |
| CCDS | Company Core Data Sheet |
| CF | cystic fibrosis |
| 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 |
| CHO | Chinese hamster ovary |
| CI | confidence interval |
| $C_{max}$ | maximum observed concentration |
| CSR | clinical study report |
| CT | computed tomography |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| DIBD | Development International Birth Date |
| $DT_{50}$ | rate of degradation |
| 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 |
| ERA | environmental risk assessment |
| EU | European Union |
| F508del | an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein |
| FDA | Food and Drug Administration (US) |
| $FEV_1$ | forced expiratory volume in 1 second |
| GI | gastrointestinal |
| GLP | Good Laboratory Practices |
| HADS | Hospital Anxiety and Depression Scale |
| hERG | human ether-à-go-go-related gene |
| HLT | high level term |
| IBD | International Birth Date |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IVA | ivacaftor |
| IV | intravenous |
| $K_d$ | distribution coefficient |
| $K_i$ | inhibition constant |
| $K_{OC}$ | organic carbon-water partitioning coefficient |
| $K_{OW}$ | octanol-water partition coefficient |
| LFT | liver function test |

| Abbreviation | Definition |
|---|---|
| LOCS | Lens Opacity Classification System |
| LUM | lumacaftor |
| LUM/IVA | LUM in combination with IVA |
| M1-IVA | metabolite of IVA, hydroxymethyl-IVA |
| M6-IVA | metabolite of IVA, IVA carboxylate |
| M28-LUM | metabolite of LUM |
| MA | marketing authorization |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRP | multi-drug resistance protein |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| MTD | maximum tolerated dose |
| N | number of subjects |
| NA | not applicable |
| OAT | organic anion transporter |
| OATP | organic anion-transporting polypeptide |
| OCT | organic cation transporter |
| OE | ophthalmological examination |
| PASS | Post-authorisation Safety Study |
| PAES | Post-authorisation Efficacy Study |
| PBT | persistence, bioaccumulation and toxicity |
| PD | person-day |
| PD | pharmacodynamic, pharmacodynamics |
| PEC | predicted environmental concentration |
| P-gp | permeability glycoprotein |
| PI | pancreatic insufficiency |
| PK | pharmacokinetic, pharmacokinetics |
| PL | Package leaflet |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PRAC | Pharmacovigilance and Risk Assessment Committee |
| PSUR | Periodic Safety Update Report |
| PY | person-year |
| q12h | every 12 hours |
| qd | once daily |
| QPPV | Qualified Person for Pharmacovigilance |
| QT | QT interval represents the duration of ventricular depolarisation and subsequent repolarisation |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate with Fridericia's correction [$QTcF = QT/RR^{0.33}$] |
| RMP | risk management plan |
| ROW | Rest of world |
| SAE | serious adverse event |
| SAWP | Scientific Advice Working Party |
| SmPC | Summary of Product Characteristics |
| SVPC | supraventricular premature complex |
| TFLs | tables, figures, and listings |
| TNF | tumour necrosis factor |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| vP | very persistent |
| VX–770 | IVA |
| VX–809 | LUM, corrector of CFTR |

# PART I Product(s) Overview

| | |
|---|---|
| **Active substance(s)** | **ORKAMBI** |
| **Pharmacotherapeutic group(s) (ATC Code)** | Other respiratory system products (R07AX30) |
| **Market Authorisation Holder** | Vertex Pharmaceuticals (Ireland) Limited |
| **Medicinal products to which this RMP refers** | lumacaftor/ivacaftor (LUM/IVA) |
| **Invented name(s) in the European Economic Area (EEA)** | ORKAMBI |
| **Market authorisation procedure** | Centralised |
| **Brief description of the product** | **LUM** is 3-(6-(1-(2,2-difluorobenzo [d] [1,3] dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl) benzoic acid.<br>**IVA** is *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. |
| | LUM is a CFTR corrector that acts directly on F508del-CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional CFTR at the cell surface. IVA is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of LUM and IVA is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. |
| **Hyperlink to the Product Information** | Summary of Product Characteristics for ORKAMBI |
| **Indication(s) in the EEA** | **Current (if applicable):** Treatment of CF in patients aged 1 year and older who are homozygous for the *F508del* mutation in the *CFTR* gene |
| | **Proposed (if applicable):** not applicable |
| Dosage in the EEA | **Current (if applicable):**<br>For patients 12 years of age and older, the recommended dose is 2 tablets (each containing 200 mg LUM and 125 mg IVA) taken orally every 12 hours (total daily dose: 800 mg LUM and 500 mg IVA).<br>For patients 6 through 11 years of age, the recommended dose is 2 tablets (each containing 100 mg LUM and 125 mg IVA) taken orally every 12 hours (total daily dose: 400 mg LUM and 500 mg IVA).<br>For patients 2 to 5 years of age, the recommended dose is:<br>•Patients weighing <14 kg: one sachet of 100 mg LUM and 125 mg IVA granules taken orally every 12 hours (total daily dose: 200 mg LUM and 250 mg IVA).<br>•Patients weighing ≥14 kg: one sachet of 150 mg LUM and 188 mg IVA granules taken orally every 12 hours (total daily dose: 300 mg LUM and 376 mg IVA).<br>For patients 1 to <2 years of age, the recommended dose is:<br>•Patients weighing 7 kg to <9 kg: one sachet of 75 mg LUM and 94 mg IVA granules taken orally every 12 hours (total daily dose: 150 mg LUM and 188 mg IVA).<br>•Patients weighing 9 kg to <14 kg: one sachet of 100 mg LUM and 125 mg IVA granules taken orally every 12 hours (total daily dose: 200 mg LUM and 250 mg IVA).<br>•Patients weighing ≥14 kg: one sachet of 150 mg LUM and 188 mg IVA granules taken orally every 12 hours (total daily dose: 300 mg LUM and 376 mg IVA).<br>•**Proposed (if applicable):**<br>Not applicable |
| **Pharmaceutical form(s) and strengths** | **Current (if applicable):**<br>•LUM 200 mg/IVA 125 mg film-coated tablet<br>•LUM 100 mg/IVA 125 mg film-coated tablet<br>•LUM 150 mg/IVA 188 mg granules in sachet<br>•LUM 100 mg/IVA 125 mg granules in sachet<br>•LUM 75 mg/IVA 94 mg granules in sachet<br>**Proposed (if applicable):**<br>•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 cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. More than 1,900 CFTR mutations have been reported to date with *F508del* being the most frequent mutation.[1]

### SI.1 Incidence

- The incidence of CF in Europe varies markedly, ranging from 1:1,353 in Ireland to 1:25,000 in Finland. Incidence for some EU countries are: Austria 1 in 3,500, Belgium 1 in 2,850, Bulgaria 1 in 3,250, Cyprus 1 in 7,914, Czech Republic 1 in 2,833, Denmark 1 in 4,700, Finland 1 in 25,000, France 1 in 4,348, Germany 1 in 3,300, Hungary 1 in 4,000, Ireland 1 in 1,353, Italy 1 in 4,238, Netherlands 1 in 4,750, Norway 1 in 8,642, Slovakia 1 in 1,800, Slovenia 1 in 3,000, Spain 1 in 3,750, Sweden 1 in 5,600, Turkey 1 in 3,000 and UK 1 in 2,381.[2,3]
- 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.[4] Approximately 1,000 new cases of CF are diagnosed each year in the US.[5]
- Approximately 1 in 3,600 children in Canada was born with CF in 2000.[6] In Canada, 120 patients (mostly children) were diagnosed with CF in 2014.[7]
- Approximately 1 in 3,050 children in Australia was born with CF annually during 1989 to 2006.[8] Approximately 1 in 3,630 children in Australia were born with CF in 2014.[9]

### SI.2 Prevalence

#### General CF Population

Approximately more than 80,000 people worldwide have CF.[10-14]

- A survey of standards of care in Europe conducted from 2007 to 2009, EuroCare CF, estimated there were 39,897 people with CF who were treated in 32 European countries.[2]

  Overall, the prevalence of CF in Europe was estimated at 0.737 per 10,000 people, ranging from 0.10 in Latvia to 2.98 in Ireland.[3] According to another survey performed by Orphanet, the prevalence of CF in the EU is 0.74 per 10,000.[15]
- In the US, there were 28,983 patients (an overall prevalence of 0.9/10,000) as reported by the national CF registry in 2015.[5]
- In Canada, over 4,128 (1.1/10,000) patients with CF had clinical records submitted by 42 clinics to the Canadian Cystic Fibrosis Registry in 2014.[7]
- According to the Australian Cystic Fibrosis Data Registry, there were 3,294 (1.4/10,000) patients with CF in 2014.[9]

#### Target Population

- Based on 2014 report from the European Cystic Fibrosis Society Patient Registry (ECFSPR) that included data on 35,582 CF patients from 26 countries, about 41% of the

patients with available genotype data were identified as homozygous for the *F508del-CFTR* mutation.[16] Across countries contributing data to the registry, proportion of homozygous *F508del-CFTR* patients ranged from about 10% in Israel to almost 70% in Denmark.[16]

- Based on 2014 ECFSPR report[16], and registry data for the UK (2015[17]) and Ireland (2014[18]), the prevalence of homozygous *F508del-CFTR* patients for countries where national registries capture ≥90% of the CF population ranges from approximately 10% to 69%.
- Based on the 2015 report from the US CFF patient registry that included data on 28,983 patients with CF, 86.4% of the patients with available genotype data had at least one *F508del* allele, with 46.1% being identified as homozygous *F508del*.[5]
- In Canada, among the over 4,128 individuals with genetic information recorded within the Canadian Cystic Fibrosis Registry in 2014, 49.9% are homozygous *F508del* and 39.8% are heterozygous *F508del*.[7]
- According to the Australian Cystic Fibrosis Data Registry in 2014, of the patients with genotype data available, 50.3% are homozygous for *F508del-CFTR*.[9]

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

CF is a genetic condition. To have CF, a person must inherit 2 copies of the defective *CFTR* gene (1 copy from each parent) that lead to dysfunctional CFTR protein.

**Age at diagnosis**

With increased rates of neonatal screening, the age at CF diagnosis is decreasing. The median age at diagnosis was 2, 4, and 2 months, as reported by the CF registries in UK[17], Ireland[18], and France[19], respectively. Across 26 European countries that contributed data to ECFSPR in 2014, the median age at diagnosis was 4 months.[16]

Similarly, in the US, the median age at diagnosis was 4 months according to 2015 registry report.[5]

In Canada, newborn screening is performed in all provinces except Quebec and 58.8% of individuals are diagnosed by 1 year of age and 66.8% by 2 years of age.[7]

**Age distribution among prevalent patients**

Of the 35,582 CF patients from 26 European countries in the ECFSPR in 2014, 51.8% were older than 18 years of age.[16]

In the US, 51.6% of all CF patients were adults 18 years or older based on 2015 annual registry report.[5] Despite the gains in median survival, the age distribution remains markedly skewed to the young. Whilst the age of US CF patients ranged from birth to a maximum age of 87.2 years, the median age was 18.6 years in 2015.[5]

In Canada in 2014, 59.7% of patients with CF were 18 years or older.[7]

**Sex**

Among CF children in Europe, a male preponderance exists at birth and persists and is reflected at all ages.[20] Based on the ECFSPR report for 2014, 52.6% out of 35,582 CF patients from 26 European countries were males.[16]

In the US, 51.6% of all CF patients were males based on 2.15 annual registry report.[5]

In Canada, based on 2014 annual patient registry report, 53.1% of patient with CF were male.[7]

**Race/ethnic origin**

CF affects all racial and ethnic groups, but is more common among Caucasians.[21] Among CF patients of all genotypes in the US, 93.8% were Caucasians, 4.6% African American, and 3.3% other races (races are not mutually exclusive as recorded in US Cystic Fibrosis Foundation).[5]

## SI.4 Main Existing Treatment Options

With the exception of drugs that target the CFTR function, such as Orkambi (LUM/IVA) and Kalydeco™ (IVA monotherapy), the main existing treatment options for CF comprise drugs or physiotherapy for the co-morbidities of CF, which may encompass the following:

**Table 1 Main Existing Treatment Options in Patients With Cystic Fibrosis**

| | |
|---|---|
| Treatment of co-morbid CF lung disease | •Airway hydration (hypertonic saline nebulisation)<br>•Mucolytics (dornase alfa)<br>•Oral antibiotics (augmentin, ciprofloxacin, azithromycin, clarithromycin)<br>•Inhaled antibiotics (tobramycin, aztreonam, colistin)<br>•Intravenous antibiotics (ceftazidime, meropenem, piperacillin-tazobactam, tobramycin, amikacin)<br>•Bronchodilators (albuterol, salmeterol)<br>•Oxygen<br>•Inhaled corticosteroids (budesonide, fluticasone)<br>•Systemic corticosteroids (prednisolone, prednisone) |
| Treatment of co-morbid CF liver disease | •Oral bile acid therapy (ursodeoxycholic acid) |
| Treatment of co-morbid CFRD | •Insulin |
| Treatment of co-morbid CF related osteoporosis and osteopenia | •Vitamin D and calcium supplementation |
| Treatment of co-morbid pancreatic insufficiency | •Pancreatic enzyme replacement<br>•Acid reduction therapy (H2-blockers; proton-pump inhibitors)<br>•Supplementation of fat-soluble vitamins (A, D, E, and K) and zinc<br>•Appetite stimulation (hydroxyzine, cyproheptadine, megestrol acetate, dronabinol) |
| Treatment of co-morbid CF arthropathy | •Systemic corticosteroids (prednisolone, prednisone)<br>•Methotrexate<br>•TNF blockers, TNF receptor blockers |
| Treatment of co-morbid anxiety and depression | •Anxiolytics<br>•Antidepressants |
| Treatment of co-morbid 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.[22] |

CF: cystic fibrosis; CFRD: cystic fibrosis related diabetes; TNF: tumour necrosis factor.

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

**Mortality**

EuroCareCF reported median age at death for 14 European countries varied 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] A female survival disadvantage exists.[23, 24]

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. 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%.[25]

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

| Country, Year | Median age at death (years) | Median predicted survival (years) | Mortality rate |
|---|---|---|---|
| United Kingdom, 2015[17] | 28 | 45.1 | 1.2% |
| Ireland, 2014[18] | 26.9 | not available | 1.7% |
| France, 2014[19] | 27.1 | not available | 1.1% |
| Germany, 2015[26] | 32.0 | not available | 1.5% |
| United States, 2015[5] | 30.1 | 41.7 | 1.5% |
| Canada, 2014[7] | 32.4 | 51.8 | 1.3% |
| Australia, 2014[9] | 27.7 | not available | 0.6% |

**Morbidity**

While mutations in the CFTR gene affect secretory glands, the organs mostly affected are the lungs, pancreas, liver/gallbladder, intestines, sinuses, and vas deferens. Other complications of CF include CFRD, bone disease, and depression.

## SI.6 Important Comorbidities

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

### *SI.6.1 CF Lung Disease*

CF lung disease is the most prevalent manifestation of CF. Natural history of CF lung disease is one of chronic progression with 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 2015, 48% of CF patients had at least one positive culture for *P. aeruginosa* (with 30% being categorized as having chronic infection and 17% as intermittent infection), for methicillin-resistant *S. aureus* (MRSA), *Burkholderia cepacia* complex, *S. aureus*, the prevalence is 26%, 3%, and 71%, respectively.[5] 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 2014 report from CF Patient Registry in Ireland, about 39% of patients aged 28 to 31 years and 34% of patients aged 12 to 23 years had at least 1 pulmonary exacerbation requiring intravenous (IV) antibiotics in 2014.[18] 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.[27-29] 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.[5] Genotype/phenotype correlations with respect to CF lung function have been described. Patients with *F508del* who are heterozygous for a second allele with residual CFTR function (*F508del/R117H* genotype, *F508del/A455E* genotype, etc.) have significantly better lung function and lower rates of *P. aeruginosa* colonisation than *F508del* homozygous patients.[30]

CF lung disease is characterized by progressive airway obstruction as measured by forced expiratory volume in 1 second ($FEV_1$). The European Epidemiologic Registry of CF collected $FEV_1$ data for 7,010 patients aged 6 years and older. Cross-sectional analysis of the 3 age groups in the study demonstrated a progressively lower $ppFEV_1$ with advancing age. Whereas children aged 6 to 12 years have mean values of $ppFEV_1$ (79.1%) reflecting mild airway obstruction, patients in the 13 to 17 years and 18 years and older age groups showed mean values of 67.8% and 54.1%, respectively, reflecting progression to moderate airway obstruction.[31] Taken together, these values reflect progressive lung disease from the earliest age at which lung function is measurable.

Based on 2015 US CF Foundation Patient Registry report, median $ppFEV_1$ was 92.9% for patients aged 6 to 17 years and 67.1% for patients 18 years and older, 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.[5]

Lung disease is the most serious complication of CF, causing the majority of mortality in patients with CF. According to the 2014 CF Registry of Ireland report, among all deaths recorded between 2002 and 2014, 67.5% were caused by respiratory/cardiac failure, and additional 6% were transplant-related.[18] In the US, 64.5% of all 2015 deaths were due to respiratory/cardiorespiratory cause and 19.2% were transplant-related.[5]

### *SI.6.2 CF Liver Disease*

Whilst 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 on ultrasound and/or hepatomegaly, or other abnormalities as follows:[32-35]

| **Hepatic abnormalities** | |
|---|---|
| Asymptomatic LFT elevations | Common (estimates vary widely) |
| Hepatomegaly | Common (estimates vary widely) |
| Steatosis and steatohepatitis | Common (23-67%) |
| Neonatal cholestasis | Not common (<2%) |
| Focal biliary cirrhosis | Common (11-72%) |
| 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 from hepatomegaly/splenomegaly, increased liver function tests (LFT), and ultrasound, the cumulative incidence of CFLD was 18%, 27%, and 28% based on long-term follow-up of CF cohorts in the US, Italy, and Israel, respectively.[36-38]

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.[37, 39]

**LFT abnormalities**

Liver abnormalities are very common among CF infants with up to 53% having elevated LFT by 3 years of age.[40] In 2 large CF patient registries in UK (2015) and Australia (2014) prevalence of abnormal LFTs in the overall CF population was reported at 11.6% and 19.1% respectively.[9, 17]

Based on the analysis of data from 376 participants of three completed multicentre CF studies with an average follow-up of 8.3 months, the incidence rates for developing any alanine aminotransferase (ALT) increase, any LFT abnormality and clinically significant LFT abnormality were estimated at 2, 3.4, and 0.4 per 100 person-months, respectively.[41]

If followed for 5 to 10 years, about 30% to 50% of CF patients would have LFT elevation on at least 1 occasion[37, 39], with up to 93% of patients with LFT abnormalities over 20 years of follow-up.[42]

Of note, whilst 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).[36]

**Clinically significant liver disease**

Whilst 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 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.[37, 40, 43] In the 2 largest CF patient registries (US and UK), prevalence of cirrhosis in 2015 was 2.7% and 2.9%, respectively.[5, 17] The prevalence of cirrhosis with portal hypertension was 1.7% in the UK registry in 2015.[17]

Two prospective studies[37, 39] reported sufficient data to estimate the incidence rates of clinically significant liver disease. Using the reported case counts and person-time from these two 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 remain the single most important non-pulmonary cause of death, accounting for about 3.3% of overall CF mortality in the US.[5]

In Ireland, among all deaths recorded between 2002 and 2014, 4.0% were caused by liver disease.[18]

During 7-year follow-up of 36 children with CFLD, 3 (8%) died from liver failure and 1 (3%) received a liver transplant. Another 3 (8%) patients died from pulmonary failure. Overall, the mortality at 7 years was 19%.[44]

### *SI.6.3 CF-Related Diabetes*

Three recent analyses estimated the prevalence of CFRD at approximately 30%. A cohort of children and adults with CF in the Netherlands reported a prevalence of CFRD of 31%[45], and 2 cohorts from Georgia and Minnesota, US, reported 31.2% and 33% CFRD, respectively.[46, 47] The prevalence increased with age, reaching 39% to 50% in adults.[45-47]

In the 2 largest CF patient registries (US and UK), prevalence of CFRD in 2015 was 21.0% and 28.0%, respectively.[5, 17] CFRD increases with age, with prevalence of 34.9% among those 18 years and older versus 6.4% among those younger than 18 years in US[5], and 32.2% among those 16 years and older versus 10.0% among those younger than 16 years in UK.[17]

The annual incidence of CFRD was estimated at 3.8% in a Danish cohort[48], 3.5% in a British cohort[49], and 2.7% in a US cohort.[47] In the Danish study the annual incidence increased with age and was 5% for patients aged 10 years or older and 9.3% for patients aged 20 years or older.[48]

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.[50]

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 PY, whilst the rate in patients with CF but without CFRD was only 1.5 (95% CI: 1.3 to 1.7) per 100 PY.[51] In a US study, the overall mortality rate for patients with CFRD was 1.8 per 100 PY, compared with 0.5 in patients with CF without diabetes.[52]

### *SI.6.4 CF-Related Osteoporosis and Osteopenia*

Bone mass is abnormally low in patients with CF, even when their treatment includes large supplements of vitamin D and calcium.[53] Low bone mineral density value was found even with daily calcium dosages of 1200 or 1500 mg.[54-57]

A recent meta-analysis of osteoporosis, osteopenia, and vertebral and nonvertebral fractures among adults with CF reported pooled prevalences of 23.5%, 38%, 14%, and 19.7%, respectively.[58] In 2015, about 5.1% and 11.9% of people with CF in the US were reported to have osteoporosis and osteopenia, respectively.[5] In the UK in 2015, 5.3% and 13.5% of all CF patients had osteoporosis and osteopenia, respectively.[17]

Fractures are very common in patients with CF, and often more than 1 fracture occurs during the life of a patient with CF.[53] Studies estimated that fracture rate was increased 2-fold in women aged 17 to 34 years and in men aged 25 to 45 years, as compared to the general population.[57]

Kyphosis with and angle greater than 40 was diagnosed in 19% of patients with CF overall. These cases occurred in 77% of female and 36% of male patients over 15 years of age.[57, 59]

### *SI.6.5 Pancreatic Insufficiency*

PI leading to steatorrhoea, nutrient malabsorption, 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. Malnourishment is associated with worsening lung function in children with CF and is an independent predictor of mortality in

this population[60-62]. Though patients diagnosed through newborn screening may not be symptomatic at the time of diagnosis, a significant proportion are pancreatic insufficient at birth[63], 85% are pancreatic insufficient before the age of 1[64] and early treatment with pancreatic enzymes and close attention to their nutritional management have been shown to result in improved growth.[65]

Among cohorts of patients with CF in Canada and the US, 87% had PI.[66, 67] In a cohort of patients with CF over 40 years of age in the UK, 82% had PI as identified in clinical notes.[68]

Most patients with CF with functionally severe mutations on both alleles have PI.[66] In 2 separate studies of CF patients in US and Europe, PI was shown to be more frequent in homozygous *F508del* patients as compared with some of the heterozygous *F508del* patients although the difference were not all statistically significant.[30, 69]

### *SI.6.6 Anxiety and Depression*

Depression was reported in 13.8% of patients with CF in the US CF Foundation Patient Registry in 2015.[5]

In a cohort of German adult and paediatric patients with CF, 9.6% reported high levels of depressive symptoms as measured by the Hospital Anxiety and Depression Scale (HADS).[70]

Among Belgian adult patients with CF, 13% reported high levels of depressive symptoms as measured by the HADS.[71]

In France, in a study of 16 patients with CF and their marital partners, 25% of patients showed signs of depression, as measured by the Centre for Epidemiologic Studies - Depression scale.[72]

Of the adolescent patients with CF in Poland who were tested using the HADS, 19% showed signs of depressive symptoms.[73]

### *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,[74] has been reported for patients with CF since 1946. The prevalence of cor pulmonale has varied from 6% to 70% when based on post-mortem studies.[75]

Heart failure has been reported at a prevalence of 8.3% among a cohort of patients with CF in Ohio, US.[22] A case report for the first symptomatic myocardial infarction in a patient with CF has been published.[76] 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 with heart failure, the mean survival was 8 months with a median survival of 4 months.[22]

## SII Nonclinical Part of the Safety Specification

LUM has been studied extensively in nonclinical studies to determine its pharmacologic activity, characterize its pharmacokinetics (PK), and establish its toxicity profile. IVA was previously studied in a similar set of studies to support the clinical development of Kalydeco.

Several studies involving the co-administration of LUM and IVA have been conducted to support co-treatment in patients with CF who have *F508del-CFTR*.

## SII.1 Toxicity

### Single and Repeat-Dose Toxicity

Single-dose studies conducted in mice and rats suggest the acute oral toxicity of LUM to be of low order. Repeat-dose toxicity studies in mice up to 3 months (sub-chronic), rats up to 6 months (chronic), and dogs up to 12 months (chronic) in duration failed to identify any target organs of LUM-related toxicity at dose levels up to and exceeding the sub-chronic maximum tolerated doses (MTDs) established in these species. Noteworthy findings observed in both rats and dogs following repeated administration were limited to dose-related body weight decrements and dose-related minimal-to-moderate decreases in erythrocytic parameters that were regenerative in rats and non-regenerative in dogs. Noteworthy findings observed only in rats following repeated administration included the regenerative response to decreases in erythrocytic parameters (comprising an increase in circulating reticulocytes and, at high doses, extramedullary haematopoiesis in the spleen) and microscopic findings of minimal centrilobular hypertrophy in male livers at high doses considered an adaptive or compensatory response to the observed cytochrome P450 (CYP) induction. Noteworthy findings observed only in dogs following repeated administration included mortality occurring at a dose level clearly exceeding the sub-chronic MTD in this species. With the exception of those adverse effects noted at dose levels exceeding the MTD in dogs, these noteworthy findings were considered non-adverse, did not progress in severity over time, and were reversible or partially reversible.

Similar toxicity studies ranging from acute to chronic in duration were conducted previously in support of the registration of Kalydeco, which identified the liver (mice and rats) as the only IVA-related target organ of toxicity. The mechanism of hepatotoxicity is believed to be a rodent-specific phenomenon (xenobiotic overload of the liver). Additional noteworthy findings were limited to cardiovascular findings of occasional instances of atrioventricular (AV) block and a slight increase in incidence of supraventricular premature complex (SVPC) runs noted in dogs following repeated administration. AV block is a well-documented background finding in this species, and the SVPC runs were not accompanied by morphological changes in the heart or changes in health status. IVA-induced SVPC runs are believed to be due to exaggerated respiratory sinus arrhythmia, which is related to canine-specific control of heart rates and therefore would not translate to morbidity or mortality, in either dogs or humans.

Combination repeat-dose toxicity studies involving the co-administration of LUM and IVA were conducted to assess the potential for additive and/or synergistic toxicity in support of the proposed combination regimen. Studies up to 3 months in duration in rats and 28 days in duration in dogs failed to produce any unexpected toxicities or interactions. Noteworthy findings in dogs were limited to a higher incidence of non-adverse cardiovascular findings (PR prolongation, AV block, and SVPC runs) than previously noted in studies conducted with IVA alone. Data from standard 12-lead and 24-hour ambulatory electrocardiogram (ECG) monitoring in the pivotal Phase 3 studies and a thorough QT clinical study indicated that the cardiovascular risk to humans receiving therapeutic doses of LUM/IVA is low. Noteworthy findings in rats were limited to non-adverse microscopic findings of occasional small foci of erosion and necrosis in the glandular mucosa of the stomach, indicating that the combination was irritating to the gastrointestinal (GI) tract of rats. These findings were

attributed to a local irritant effect of LUM and IVA at high concentrations and are not considered relevant to humans.

Based on the available data for acute, subacute, subchronic, and chronic toxicity studies, the combination regimen is considered safe for chronic administration in humans.

**Reproductive and Developmental Toxicity**

The overall conclusions from reproductive and developmental toxicity studies evaluating LUM indicate that it is not a reproductive and/or developmental toxicant. Embryo-foetal development (EFD) studies demonstrated that LUM was not teratogenic and should not be considered a developmental toxicant in rats and rabbits. When co-administered to rats, LUM and M28-LUM did not result in toxicity to male or female reproductive systems or have effects on early embryonic development. Similarly, co-administration of LUM and M28-LUM to rats did not produce any adverse effects on maternal and/or $F_1$-generation prenatal/postnatal development. M28-LUM produced developmental toxicities (foetal malformations) only at extremely high doses (100-fold clinical exposures) which resulted in significant maternal toxicity in rats.

When evaluated in a similar set of studies to support registration of Kalydeco, IVA was considered to have only minimal effects on female reproduction and foetal development in rats attributable to significant maternal toxicity, and that it is associated with ocular toxicities in juvenile animals. IVA was not teratogenic in rats and rabbits, with developmental findings being limited to effects on foetal body weight and small increases in common variations in skeletal development noted only in rats at a dose resulting in significant maternal toxicity. IVA had no effects on the male rat reproductive system, whereas effects on female rat reproduction and on early embryonic development were noted only at maternally toxic doses. While maternal toxicity in rats had effects on foetal development and growth of offspring, there were no adverse effects on learning and memory or on reproductive capacity in offspring.

Juvenile toxicity studies conducted with IVA identified the eye (lens opacities/cataracts) as a target organ of toxicity. Cataracts were not detected in the eyes of developing rat foetuses from the EFD study with IVA or in repeat-dose toxicity studies conducted in older mice, rats, or dogs, including chronic toxicity studies using rats as young as 7 weeks old at dosing initiation and dogs as young as 3.5 months old at dosing initiation.

Placental and lacteal transfer studies have demonstrated that LUM and to a lesser extent IVA cross the placental barrier and both are secreted in the milk of lactating rats. It should be assumed that LUM and IVA will be secreted in human breast milk. Based on the available data, the overall reproductive and developmental risk associated with the proposed combination regimen in subjects 12 years of age and older is considered low.

**Genotoxicity**

LUM and IVA were nonmutagenic and nonclastogenic in the ICH standard battery of genotoxicity tests (bacterial reverse mutation assay, Chinese hamster ovary (CHO) cell chromosomal aberration test, and mouse micronucleus assay. M28-LUM was also negative in the bacterial reverse mutation assay and CHO cell chromosomal aberration test.

**Carcinogenicity**

Consistent with the fact that LUM is non-genotoxic and the lack of pre-neoplastic or other proliferative lesions detected in any tissue in the subchronic and chronic studies in mice, rats, and dogs establishing the repeat-dose toxicity profile of LUM, LUM was non-carcinogenic in the 26-week Tg.rasH2 transgenic mouse carcinogenicity assay and non-carcinogenic in a 2-

year rat carcinogenicity study. Consistent with its non-genotoxic and subchronic and chronic repeat-dose toxicity profiles, IVA was also non-carcinogenic in the 2-year rodent bioassays previously conducted in support of the registration of Kalydeco. Based on the available data, the overall carcinogenic risk associated with the combination regimen is considered low.

## SII.2 Safety Pharmacology

LUM and IVA have been studied extensively in GLP-compliant, nonclinical studies to determine their pharmacological activity, metabolism, PK, and safety.

### Off-target effect

Consistent with a specific action on CFTR, LUM does not correct several other misfolded or normally folded non-CFTR proteins, including other membrane-localized ion channels and ATP-binding cassette transporters that exhibit defects in processing and trafficking. The results of exploratory screening studies evaluating binding affinities to a variety of receptors, channels, and enzymes demonstrated that LUM and M28-LUM (pharmacologically inactive minor but disproportionate human metabolite), are highly selective with effects being limited to LUM-mediated binding and functional antagonism of the human thromboxane A2 receptor. A similar panel of exploratory binding affinity studies evaluating the potential for secondary pharmacodynamic (PD) effects associated with IVA, conducted previously in support of the registration of Kalydeco and pertinent given the proposed combination regimen, also 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-IVA (a major human metabolite of IVA) 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 187 assays conducted.

In therapy with LUM/IVA, a higher dose of IVA (250 mg every 12 hours [q12h]) is used than in IVA monotherapy (150 mg q12h), and the exposure of M6-IVA is higher in LUM/IVA therapy than that in IVA monotherapy (Kalydeco). As demonstrated in the clinical studies, LUM/IVA therapy is well tolerated, and the higher exposure of M6-IVA does not appear to be a clinically relevant safety concern.

Results from a comprehensive program of safety pharmacology studies conducted to assess LUM's effects in vital organ systems and potential for adverse PD effects suggest a low potential for LUM to elicit effects on neurobehavioral and physiological processes, effects on respiratory rate or tidal volume, effects on cardiovascular parameters, or effects on GI motility. With exception of notable decreases in rat GI motility considered not relevant at therapeutic doses in humans, results from a similar set of safety pharmacology studies conducted in support of the registration of Kalydeco suggest a low potential for IVA to elicit effects on those same endpoints mentioned above. A set of follow-on studies evaluating the potential effects of M6-IVA on cardiac ion channels demonstrated a low likelihood for cardiac effects to be associated with this major circulating metabolite.

Overall, results from safety pharmacology studies evaluating LUM and IVA, and results from secondary PD and selectivity studies suggest a high degree of selectivity and a low potential to have detrimental effects on vital function when LUM and IVA are administered in combination.

### Pharmacokinetics

Animal studies characterizing the PK profile of LUM demonstrated that it was well absorbed, widely distributed across different tissues, and predominantly excreted unchanged in the faeces with a small fraction of the dose cleared following metabolism via multiple pathways.

Because LUM is eliminated predominantly unchanged in the faeces, biliary secretion by transporters may be involved. LUM was determined to be a substrate for breast cancer resistance protein (BCRP) but not of multi-drug resistance related protein (MRP) 2. Thus, BCRP-mediated efflux of LUM could potentially contribute to LUM's hepatobiliary/faecal elimination as intact parent.

LUM metabolic profiles were qualitatively similar in all species studied, except for M28-LUM which was observed at higher levels in humans. Although initially categorized as a major metabolite, as the relevant clinical doses increased during the clinical development program, the relative amount of M28-LUM to LUM became lower and M28-LUM was classified as a minor but disproportionate and pharmacologically inactive human metabolite. The PK profile of IVA was previously established and demonstrated that it was well absorbed, widely distributed across different tissues, extensively metabolized and primarily eliminated in faeces. IVA was primarily metabolized by oxidation in all species to its major circulating metabolites M1-IVA and M6-IVA. The plasma protein binding of LUM and IVA and metabolites is high across all species including human where they are primarily bound to human serum albumin. Based on the high permeability of LUM and IVA in Caco-2 cell-based assay and oral bioavailability in animals ranging from 30% to 100%, the human absorption of LUM and IVA was predicted to be high after oral administration. In humans, LUM and IVA were bioavailable and had good exposures following oral administration of a fixed dose combination tablet.

**Mechanisms for drug interactions**

Based on in vitro results, LUM has the potential to induce CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19; however, inhibition of CYP2C8 and CYP2C9 has also been observed in vitro. In vitro data suggests that CYP3A4 may be involved in the metabolism of LUM. LUM may reduce exposures of medicinal products that are sensitive substrates of CYP3A or CYP3A substrates with narrow therapeutic index.

Based on in vitro results that showed permeability glycoprotein (P-gp) inhibition and pregnane-X-receptor activation, LUM has the potential to both inhibit and induce P-gp. A clinical study with IVA monotherapy showed that IVA is a weak inhibitor of P-gp. Therefore, LUM/IVA therapy may alter the exposure of P-gp substrates.

In vitro studies of the potential for LUM to inhibit other transporter systems showed that LUM has the potential to inhibit BCRP and the renal uptake transporters organic anion transporter (OAT) 1 and OAT3, but not organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, or OCT2.

In vitro studies indicated that IVA is a substrate of CYP3A, an inhibitor of P-gp, a potential inhibitor of cytochrome P450 - enzyme subfamilies CYP2C8, CYP2C9, and CYP3A, 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 IVA and rosiglitazone, a CYP2C8 probe, and coupled with the in vitro inhibition constant ($K_i$) for CYP2C9 being 10-fold higher than that for CYP2C8, no interaction with CYP2C9 is expected and so was not studied further. IVA has the potential to inhibit BCRP, but not OAT1, OAT3, OCT1, or OCT2.

## SII.3 Other Toxicity-Related Information or Data

**Environmental Risk**

Environmental risks assessments (ERAs) were conducted for LUM and IVA.

*Lumacaftor (or VX-809)*

Phase I: A Phase I estimation of exposure showed that an evaluation of the persistence, bioaccumulation and toxicity (PBT) of VX-809 was not warranted based on its octanol/water partition coefficient (log Kow <4.5). The worst-case scenario for the Phase I predicted environmental concentration of VX-809 in surface water ($PEC_{SURFACEWATER}$) was calculated using a refined market penetration factor. The $PEC_{SURFACEWATER}$ of 0.059 µg/L exceeded the trigger value for a Phase II Tier A assessment of its environmental fate and effects (>0.01µg/L).

Phase II Tier A and B: The outcome of the Phase II Tier A assessment confirmed that VX-809 is unlikely to represent a risk to surface water, groundwater or to microorganisms. The distribution coefficient (Kd) in 2 sewage sludges was <3,700 L/kg and the soil organic carbon-water partitioning coefficient (Koc) was <10,000 L/kg. Therefore, VX-809 is unlikely to reach the terrestrial compartment as a result of spreading of sewage sludge onto agricultural land. The rate of dissipation of VX-809 from water into sediment was 8.9 and 13 days in the two systems. The rate of degradation (DT50) in the total systems was 207 and 155 days. As one of these half-lives was >180 days, VX-809 should be considered as very persistent. The outcome of the Phase II Tier B test confirmed that VX-809 is unlikely to represent a risk to sediment organisms or to the terrestrial environment.

Overall, VX-809 is unlikely to represent a risk to the aquatic or terrestrial environment.

*Ivacaftor (or VX-770)*

The ERA report for VX-770 provides an environmental risk assessment for VX-770 in combination with VX-661 (Symkevi™). The maximum daily dosage is 300 mg, administered orally.

Phase I: A Phase I estimation of exposure showed that an evaluation of the PBT of VX-770 was required (log Kow >4.5). These studies were conducted under Phase II Tier A and B. The worst-case scenario for the Phase I $PEC_{SURFACEWATER}$ of VX-770 was calculated to be 0.0066 µg/L in Kalydeco (tablets and granules) and 0.03675 µg/L in combination with VX-809. In combination with VX-661, the $PEC_{SURFACEWATER}$ of VX-770 was calculated to be 0.0375. Thus, the combined $PEC_{SURFACEWATER}$ for VX-770 is 0.081 µg/L. The total $PEC_{SURFACEWATER}$ of 0.081 µg/L exceeds the trigger value for a Phase II Tier A assessment of its environmental fate and effects (>0.01µg/L).

Phase II Tier A: The outcome of the Phase II Tier A environmental effects assessment in algae, *Daphnia*, fish and microorganisms confirmed that VX-770 is unlikely to represent a risk to surface water, groundwater or to microorganisms. The Kd in 2 sewage sludges was >3,700 L/kg and the Koc was >10,000 L/kg. Therefore, VX-770 is likely to reach the terrestrial compartment as a result of spreading of sewage sludge onto agricultural land. The Phase II Tier B terrestrial studies were, therefore, conducted. Since the ready biodegradability of VX-770 was not determined and more than 10% of the drug was detected in sediment after 14 days, an investigation of the effects of VX-770 on sediment organisms (chironomids) was conducted. The rate of dissipation of VX-770 from water into sediment was 4.4 and 1.7 days in the two systems. The $DT_{50}$ in the total systems was 581 and 123 days. As one of these half-lives was >180 days, VX-770 should be considered as very persistent. Preliminary results indicate that VX-770 does not bioaccumulate in fish.

Phase II Tier B: Preliminary results indicate that VX-770 had no impact on nitrogen transformation in soil. VX-770 is unlikely to represent a risk to sediment dwelling organisms. The $DT_{50}$ of VX-770 in four soils was 166 to 316 days. The geometric mean and three of these half-lives are all higher than 180 days and therefore VX-770 meets the criterion for

very persistent (vP) in soil. The outcome of the Phase II Tier B terrestrial effects assessment in microorganisms, plants, earthworms, and Collembola confirmed that VX-770 is unlikely to represent a risk to the terrestrial environment.

Overall, VX-770 is unlikely to represent a risk to the aquatic or terrestrial environment.

## SIII Clinical Trial Exposure

Table 2 summarises the cumulative subject exposure data since the Development International Birth Date (DIBD; 14 November 2007) in Phase 1, 2, and 3 clinical studies sponsored by the MAH.

Cumulatively, an estimated 2,410 subjects have been exposed to at least 1 dose of active treatment (i.e., either LUM monotherapy or LUM/IVA combination therapy) in clinical studies; 1,933 were subjects with CF and 419 were healthy subjects in Phase 1, 2, and 3 studies. By comparison, a total of 743 subjects have been exposed to at least 1 dose of placebo in the LUM development programme; 632 were subjects with CF and 111 were healthy subjects (Table 2).

Exposures in the LUM/IVA development clinical studies were calculated using PY and person-days, as applicable. As shown in Table 2, subjects were exposed to active treatment in Phase 1, 2, and 3 clinical studies for approximately 2,767.3 PY, in comparison to 251.9 PY for the placebo subjects.

The cumulative subject exposure by duration, age, sex, and racial group are provided in Table 3, Table 4, Table 5, and Table 6, respectively. [redacted] the [redacted] were aged ≥18 to <65 years and [redacted] The cumulative subject exposures to active treatment were [redacted] between [redacted] subjects. Estimates were based on actual exposure from completed and ongoing studies where data are available.

**Table 2 Summary of Exposure in the LUM Clinical Development Programme by Dose**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| **Dose** | **N** | **Total Exposure (PY)** | **N** | **Total Exposure (PY)** | **N** | **Total Exposure (PY)** |
| **Total** | **510** | **17.9** | **2021** | **3024.1** | **2531** | **3042.0** |
| **Active (Combination and Monotherapy)** | **419** | **13.4** | **1933** | **2753.9** | **2352** | **2767.3** |
| **Combination (LUM/IVA)** | **282** | **9.3** | **1846** | **2739.8** | **2128** | **2749.1** |
| LUM 400 mg q12h/IVA 250 mg q12h | 0 | NA | 845 | 1163.9 | 845 | 1163.9 |
| LUM 600 mg qd/IVA 250 mg q12h | 55 | 1.0 | 585 | 959.8 | 640 | 960.8 |
| LUM 200 mg q12h/IVA 250 mg q12h | 77 | 3.8 | 276 | 422.7 | 353 | 426.5 |
| LUM 150 mg q12h/IVA 188 mg q12h | 0 | NA | 116 | 131.2 | 116 | 131.2 |
| LUM 100 mg q12h/IVA 125 mg q12h | 0 | NA | 94 | 57.1 | 94 | 57.1 |
| LUM 75 mg q12h/IVA 94 mg q12h | 0 | NA | 8 | 0.5 | 8 | 0.5 |
| Other LUM/IVA | 199 | 4.5 | 106 | 4.6 | 305 | 9.0 |
| **Monotherapy (LUM)** | **187** | **4.1** | **218** | **14.1** | **405** | **18.2** |
| LUM 400 mg q12h | 0 | NA | 11 | 0.8 | 11 | 0.8 |
| LUM 600 mg qd | 38 | 0.3 | 42 | 3.0 | 80 | 3.3 |

**Table 2 Summary of Exposure in the LUM Clinical Development Programme by Dose**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Dose | N | Total Exposure (PY) | N | Total Exposure (PY) | N | Total Exposure (PY) |
| LUM 1200 mg qd | 8 | 56.0 (PD) | 0 | NA | 8 | 56.0 (PD) |
| LUM 1000 mg qd | 8 | 56.0 (PD) | 0 | NA | 8 | 56.0 (PD) |
| Other LUM | 162 | 3.5 | 165 | 10.3 | 327 | 13.8 |
| **Total Placebo** | **111** | **4.5** | **632** | **247.4** | **743** | **251.9** |

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: lumacaftor in combination with ivacaftor; NA: not applicable; PD: person-day; PY: person-year; q12h: every twelve hours; qd: once daily; TFLs: tables, figures, and listings

Notes: N: Number of subjects in the Safety Set (who have received any amount of lumacaftor alone (monotherapy), LUM/IVA, or placebo and had the dosing information **included in the clinical database by 19 May 2021**).

[a] Including the following studies with the final CSR TFLs available: 001, 003 to 010, 012, and 014. In Study 010, 12 subjects with hepatic impairment who received LUM 200 mg q12h/IVA 250 mg q12h are included.

[b] Including the following studies with the final CSR TFLs available: 002, 011, 101 to 106, 109 to 111, 115, and 116 as well as the following ongoing studies: 121, 122 (Parts A and B), and 124. For Study 121, the exposure is estimated, given that the study is still blinded.

**Table 3 Summary of Exposure in the LUM Clinical Development Programme by Duration**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Duration | N | Total Exposure (PY) | N | Total Exposure (PY) | N | Total Exposure (PY) |
| **Total** | **510** | **17.9** | **2021** | **3024.1** | **2531** | **3042.0** |
| 1 day | 10 | 10.0 (PD) | 6 | 6.0 (PD) | 16 | 16.0 (PD) |
| >1 day to <4 weeks | 424 | 11.4 | 135 | 6.2 | 559 | 17.5 |
| ≥4 to < 8 weeks | 76 | 6.5 | 131 | 13.0 | 207 | 19.5 |
| ≥8 to <24 weeks | 0 | NA | 191 | 47.4 | 191 | 47.4 |
| ≥24 to <48 weeks | 0 | NA | 211 | 125.3 | 211 | 125.3 |
| ≥48 to <72 weeks | 0 | NA | 65 | 71.4 | 65 | 71.4 |
| ≥72 weeks to <96 weeks | 0 | NA | 121 | 197.1 | 121 | 197.1 |
| ≥96 weeks | 0 | NA | 1161 | 2563.7 | 1161 | 2563.7 |
| **Active (Combination and Monotherapy)** | **419** | **13.4** | **1933** | **2753.9** | **2352** | **2767.3** |
| 1 day | 11 | 11.0 (PD) | 8 | 8.0 (PD) | 19 | 19.0 (PD) |
| >1 day to <4 weeks | 348 | 8.7 | 118 | 5.2 | 466 | 13.8 |
| ≥4 to < 8 weeks | 60 | 4.7 | 119 | 12.1 | 179 | 16.9 |
| ≥8 to <24 weeks | 0 | NA | 195 | 51.1 | 195 | 51.1 |
| ≥24 to <48 weeks | 0 | NA | 178 | 107.6 | 178 | 107.6 |
| ≥48 to <72 weeks | 0 | NA | 94 | 98.5 | 94 | 98.5 |
| ≥72 weeks to <96 weeks | 0 | NA | 316 | 521.4 | 316 | 521.4 |
| ≥96 weeks | 0 | NA | 905 | 1957.8 | 905 | 1957.8 |
| **Combination (LUM/IVA)** | **282** | **9.3** | **1846** | **2739.8** | **2128** | **2749.1** |
| 1 day | 2 | 2.0 (PD) | 6 | 6.0 (PD) | 8 | 8.0 (PD) |
| >1 day to <4 weeks | 266 | 8.1 | 117 | 4.5 | 383 | 12.6 |
| ≥4 to <8 weeks | 14 | 1.2 | 103 | 9.5 | 117 | 10.7 |
| ≥8 to <24 weeks | 0 | NA | 127 | 40.4 | 127 | 40.4 |
| ≥24 to <48 weeks | 0 | NA | 178 | 107.6 | 178 | 107.6 |
| ≥48 to <72 weeks | 0 | NA | 94 | 98.5 | 94 | 98.5 |
| ≥72 weeks to <96 weeks | 0 | NA | 316 | 521.3 | 316 | 521.3 |
| ≥96 weeks | 0 | NA | 905 | 1957.8 | 905 | 1957.8 |

**Table 3 Summary of Exposure in the LUM Clinical Development Programme by Duration**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Duration | N | Total Exposure (PY) | N | Total Exposure (PY) | N | Total Exposure (PY) |
| **Monotherapy (LUM)** | **187** | **4.1** | **218** | **14.1** | **405** | **18.2** |
| 1 day | 9 | 9.0 (PD) | 2 | 2.0 (PD) | 11 | 11.0 (PD) |
| >1 day to <4 weeks | 178 | 4.1 | 76 | 3.1 | 254 | 7.2 |
| ≥4 to <8 weeks | 0 | NA | 140 | 11.0 | 140 | 11.0 |
| **Placebo** | **111** | **4.5** | **632** | **247.4** | **743** | **251.9** |
| 1 day | 19 | 19.0 (PD) | 0 | 0 (PD) | 19 | 19.0 (PD) |
| >1 day to <4 weeks | 76 | 2.6 | 28 | 1.5 | 104 | 4.1 |
| ≥4 to <8 weeks | 16 | 1.8 | 38 | 4.5 | 54 | 6.3 |
| ≥8 to <24 weeks | 0 | NA | 244 | 84.4 | 244 | 84.4 |
| ≥24 to <48 weeks | 0 | NA | 307 | 143.6 | 307 | 143.6 |
| ≥48 to <72 weeks | 0 | NA | 14 | 13.5 | 14 | 13.5 |

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: lumacaftor in combination with ivacaftor; NA: not applicable; PD: person-day; PY: person-year; q12h: every 12 hours; TFLs: tables, figures, and listings

Notes: N: Number of subjects in the Safety Set (who have received any amount of lumacaftor alone (monotherapy), LUM/IVA, or placebo and had the dosing information **included in the clinical database by 19 May 2021**).

[a] Including the following studies with the final CSR TFLs available: 001, 003 to 010, 012, and 014. In Study 010, 12 subjects with hepatic impairment who received LUM 200 mg q12h/IVA 250 mg q12h are included.

[b] Including the following studies with the final CSR TFLs available: 002, 011, 101 to 106, 109 to 111, 115, and 116 as well as the following ongoing studies: 121, 122 (Parts A and B), and 124. For Study 121, the exposure is estimated, given that the study is still blinded.

**Table 4 Summary of Exposure in the Lumacaftor Clinical Development Programme by Age**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Sex Age (Years) | N | Exposure (PY) | N | Exposure (PY) | N | Exposure (PY) |
| **Total** | **510** | **17.9** | **2021** | **3024.1** | **2531** | **3042.0** |
| ≥12 to <24 months | 0 | NA | 68 | 42.3 | 68 | 42.3 |
| ≥2 to <6 years | 0 | NA | 113 | 204.0 | 113 | 204.0 |
| ≥6 to <12 years | 0 | NA | 265 | 543.6 | 265 | 543.6 |
| ≥12 to <18 years | 0 | NA | 294 | 587.1 | 294 | 587.1 |
| ≥18 to <65 years | 509 | 17.9 | 1281 | 1647.0 | 1790 | 1664.9 |
| ≥65 years | 1 | 3.0 (PD) | 0 | NA | 1 | 3.0 (PD) |
| **Active (Combination and Monotherapy)** | **419** | **13.4** | **1933** | **2753.9** | **2352** | **2767.3** |
| ≥12 to <24 months | 0 | NA | 68 | 42.3 | 68 | 42.3 |
| ≥2 to <6 years | 0 | NA | 112 | 165.7 | 112 | 165.7 |
| ≥6 to <12 years | 0 | NA | 250 | 481.8 | 250 | 481.8 |
| ≥12 to <18 years | 0 | NA | 302 | 559.9 | 302 | 559.9 |
| ≥18 to <65 years | 418 | 13.4 | 1201 | 1504.2 | 1619 | 1517.6 |
| ≥65 years | 1 | 3.0 (PD) | 0 | NA | 1 | 3.0 (PD) |
| **Combination (LUM/IVA)** | **282** | **9.3** | **1846** | **2739.8** | **2128** | **2749.1** |
| ≥12 to <24 months | 0 | NA | 68 | 42.3 | 68 | 42.3 |
| ≥2 to <6 years | 0 | NA | 112 | 165.7 | 112 | 165.7 |
| ≥6 to <12 years | 0 | NA | 250 | 481.8 | 250 | 481.8 |
| ≥12 to <18 years | 0 | NA | 302 | 559.9 | 302 | 559.9 |
| ≥18 to <65 years | 281 | 9.3 | 1114 | 1490.0 | 1395 | 1499.3 |

**Table 4 Summary of Exposure in the Lumacaftor Clinical Development Programme by Age**

| Sex / Age (Years) | Healthy Subjects[a] N | Healthy Subjects[a] Exposure (PY) | Subjects With CF[b] N | Subjects With CF[b] Exposure (PY) | Overall N | Overall Exposure (PY) |
|---|---|---|---|---|---|---|
| ≥65 years | 1 | 3.0 (PD) | 0 | NA | 1 | 3.0 (PD) |
| **Monotherapy (LUM)** | **187** | **4.1** | **218** | **14.1** | **405** | **18.2** |
| ≥18 to <65 | 187 | 4.1 | 218 | 14.1 | 405 | 18.2 |
| **Placebo** | **111** | **4.5** | **632** | **247.4** | **743** | **251.9** |
| ≥12 to <24 months | 0 | NA | 0 | 0.0 | 0 | 0.0 |
| ≥2 to <6 years | 0 | NA | 17 | 15.5 | 17 | 15.5 |
| ≥6 to <12 years | 0 | NA | 101 | 45.2 | 101 | 45.2 |
| ≥12 to <18 years | 0 | NA | 98 | 43.8 | 98 | 43.8 |
| ≥18 to <65 years | 111 | 4.5 | 416 | 142.9 | 527 | 147.4 |
| ≥65 years | 0 | NA | 0 | 0.0 (PD) | 0 | 0.0 (PD) |

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: lumacaftor in combination with ivacaftor; NA: not applicable; PD: person-day; PY: person-year; q12h: every 12 hours; TFLs: tables, figures, and listings

Notes: N = number of subjects in the Safety Set (who have received any amount of LUM alone [monotherapy], LUM/IVA, or placebo and had the dosing **information included in the clinical database by 19 May 2021**).

[a] Including the following studies with the final CSR TFLs available: 001, 003 to 010, 012, and 014. In Study 010, 12 subjects with hepatic impairment who received LUM 200 mg q12h/IVA 250 mg q12h are included.

[b] The following studies have completed final CSRs: 002, 011 (Parts A and B), 101-106, 109, 110, 111, 115 (Parts A and B), and 116. The following studies are ongoing or have uncompleted final CSRs: 121, 122 (Parts A and B), and 124. For Study 121, the exposure is estimated, given that the study is still blinded.

**Table 5 Summary of Cumulative Exposure in the Lumacaftor Clinical Development Program by Sex**

| Sex | Healthy Subjects[a] N | Healthy Subjects[a] Exposure (PY) | Subjects With CF[b] N | Subjects With CF[b] Exposure (PY) | Overall[c] N | Overall[c] Exposure (PY) |
|---|---|---|---|---|---|---|
| **Total** | **510** | **17.9** | **2021** | **3024.1** | **2531** | **3042.0** |
| [redacted] | | | | | | |
| **Active (Combination and Monotherapy)** | **419** | **13.4** | **1933** | **2753.9** | **2352** | **2767.3** |
| [redacted] | | | | | | |
| **Combination (LUM/IVA)** | **282** | **9.3** | **1846** | **2739.8** | **2128** | **2749.1** |
| [redacted] | | | | | | |
| **Monotherapy (LUM)** | **187** | **4.1** | **218** | **14.1** | **405** | **18.2** |
| [redacted] | | | | | | |
| **Placebo** | **111** | **4.5** | **632** | **247.4** | **743** | **251.9** |
| [redacted] | | | | | | |

**Table 5 Summary of Cumulative Exposure in the Lumacaftor Clinical Development Program by Sex**

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

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: lumacaftor in combination with ivacaftor; PY: person-year; q12h: every 12 hours; TFLs: tables, figures, and listings

Notes: N = number of subjects in the Safety Set (who have received any amount of LUM alone [monotherapy], LUM/IVA, or placebo and had the dosing information **included in the clinical database by 19 May 2021**).

[a] Including the following studies with the final CSR TFLs available: 001, 003 to 010, 012, and 014. In Study 010, 12 subjects with hepatic impairment who received LUM 200 mg q12h/IVA 250 mg q12h are included.

[b] The following studies have completed final CSRs: 002, 011 (Parts A and B), 101-106, 109, 110, 111, 115 (Parts A and B), and 116. The following studies are ongoing or have uncompleted final CSRs: 121, 122 (Parts A and B), and 124. For Study 121, the exposure is estimated, given that the study is still blinded.

**Table 6 Summary of Exposure in the LUM Clinical Development Programme by Racial Group**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| **Race** | **N** | **Total Exposure (PY)** | **N** | **Total Exposure (PY)** | **N** | **Total Exposure (PY)** |
| **Total** | **510** | **17.9** | **2021** | **3024.1** | **2531** | **3042.0** |
| [redacted] | | | | | | |
| **Active (Combination and Monotherapy)** | **419** | **13.4** | **1933** | **2753.9** | **2352** | **2767.3** |
| [redacted] | | | | | | |
| **Combination (LUM/IVA)** | **282** | **9.3** | **1846** | **2739.8** | **2128** | **2749.1** |
| [redacted] | | | | | | |
| **Monotherapy (LUM)** | **187** | **4.1** | **218** | **14.1** | **405** | **18.2** |
| [redacted] | | | | | | |

**Table 6 Summary of Exposure in the LUM Clinical Development Programme by Racial Group**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Race | N | Total Exposure (PY) | N | Total Exposure (PY) | N | Total Exposure (PY) |
| [redacted] | | | | | | |
| Placebo | 111 | 4.5 | 632 | 247.4 | 743 | 251.9 |
| [redacted] | | | | | | |

CF: cystic fibrosis; CSR: clinical study report; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: lumacaftor in combination with ivacaftor; NA: not applicable; PD: person-day; PY: person-year; q12h: every 12 hours; TFLs: tables, figures, and listings

Notes: N: Number of subjects in the Safety Set (who have received any amount of LUM alone (monotherapy), LUM/IVA, or placebo and had the dosing information included in the clinical database by 19 May 2021).

[redacted]

[a] Including the following studies with the final CSR TFLs available: 001, 003 to 010, 012, and 014. In Study 010, 12 subjects with hepatic impairment who received LUM 200 mg q12h/IVA 250 mg q12h are included.

[b] Including the following studies with the final CSR TFLs available: 002, 011, 101 to 106, 109 to 111, 115, and 116 as well as the following ongoing studies: 121,122 (Parts A and B), and 124. For Study 121, the exposure is estimated, given that the study is still blinded.

# 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 | LUM/IVA did not show unfavourable effects on conditions described in the exclusion criterion. LUM/IVA improves overall pulmonary condition ($ppFEV_1$ and rate of pulmonary exacerbations, particularly those requiring IV antibiotic treatment and hospitalisation) 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 | Not applicable |

| | |
|---|---|
| **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? | No |
| Rationale | Hepatobiliary Events, including abnormal liver function tests, are addressed as an important identified risk rather than missing information. |
| **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 LUM, IVA, and their metabolites, the use of LUM/IVA in patients with renal impairment is not considered missing information. |
| **History of prolonged QT/QTcF interval (>450 ms)** | |
| Reason for exclusion | As a precautionary measure, patients with history of prolonged QT interval were excluded from clinical studies. |
| Is it to be considered missing information? | No |
| Rationale | Based on the ECG results from the thorough QT study and other clinical studies, LUM/IVA did not demonstrate any potential to prolong QT intervals. In addition, the incidence of cardiac events occurred at a small and similar incidence in both LUM/IVA and placebo groups. Therefore, LUM/IVA use in patients with history of prolonged QT interval is not considered 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 as 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 trials with LUM/IVA as the transplanted lungs have normal CFTR. |
| Is it to be considered missing information? | Yes |
| Rationale | Not applicable |
| **Colonisation with organisms associated with a more rapid decline in pulmonary status** | |
| Reason for exclusion | Conditions described in this exclusion criterion, as with any other pulmonary-related adverse conditions, may interfere with study results. |
| Is it to be considered missing information? | No |
| Rationale | LUM/IVA did not show unfavourable effects in patients with bacteria colonisation. LUM/IVA improves overall pulmonary condition ($ppFEV_1$ and rate of pulmonary exacerbations, particularly those requiring IV antibiotic treatment and hospitalisation) in patients with CF. |
| **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; concomitant use of LUM/IVA with a CYP3A inducer or inhibitor may alter the exposure of IVA in combination therapy. |
| Is it to be considered missing information? | No |
| Rationale | Potential interactions with CYP3A inducers or inhibitors were addressed as an important potential risk for LUM/IVA rather than missing information. |
| **Evidence of clinically significant cataract or lens opacity at screening** | |
| Reason for exclusion | To avoid ascertainment bias in the interpretation of results, patients with clinically significant lens opacities were excluded due to the cataract findings in the juvenile rats study with IVA. |
| Is it to be considered missing information? | No |
| Rationale | Cataracts is addressed as an important potential risk rather than missing information. |

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450; ECG: electrocardiogram; IV: intravenous; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: LUM in combination with IVA; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; QT: QT interval represents the duration of ventricular depolarisation and subsequent repolarisation; QTcF: QT interval corrected for heart rate with Fridericia's correction

## 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 | 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, defined as abnormalities ≥3 × ULN in any 3 or more of the following: serum AST, serum ALT, GGT, serum alkaline phosphatase, or total bilirubin, were excluded.<br>Study 010 was conducted to evaluate the effect of moderate hepatic impairment on PK of LUM/IVA, in compliance with EMA and US FDA guidelines.<br>The total exposures of LUM and IVA at steady state were higher ($AUC_\tau$ by approximately 50% and $C_{max}$ by approximately 30%) in subjects with moderate hepatic impairment compared with matched healthy subjects. Following multiple doses of LUM 200 mg q12h/IVA 250 mg q12h, no subjects with moderate hepatic impairment had liver related AEs, and 1 subject had a treatment emergent AST elevation >3 × ULN.<br>The placebo-controlled Phase 3 clinical studies included 7 subjects with cirrhosis and/or portal hypertension who received LUM/IVA. Among these 7 subjects, 6 completed treatment without any transaminase or hepatobiliary AEs or elevated liver enzymes (>3 × ULN), and 1 subject had worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy. The event occurred within 5 days of the start of dosing and resolved following treatment discontinuation.<br>Use of LUM/IVA in patients with advanced liver disease is addressed within the scope of the important identified risk of hepatobiliary events. |
| Patients with renal impairment | Subjects with a history of abnormal renal function (at screening), defined as creatinine clearance <89 mL/min/1.73 $m^2$ using the Counahan-Barratt equation (for subjects aged 12 to 17 years) or <50 mL/min using the Cockcroft-Gault equation (for subjects aged 18 years or older), were excluded from clinical studies. 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.<br>In the human absorption, distribution, metabolism, excretion study (Study 004), there was minimal elimination of LUM and its metabolites in urine (only 8.6% of total radioactivity was recovered in the urine, with 0.18% as unchanged parent). For M28-LUM, the major plasma metabolite of LUM, urinary excretion was also negligible (0.01% to 0.14% following a single oral dose of 200 mg).<br>In Study 770-003, the majority of IVA (86.1%) is excreted in the faeces after metabolic conversion. The major metabolites, M1-IVA and M6-IVA, accounted for approximately 65% of the total dose excreted with 22% as M1-IVA and 43% as M6-IVA. Urinary excretion of IVA as unchanged parent was negligible (<0.01%) and was minimal for IVA plus metabolites, 6.6% of the dose.<br>Collectively, these results suggest that renal clearance plays a minimal role in the elimination of LUM and IVA.<br>Use of LUM/IVA in patients with renal impairment is not considered missing information. |

| Type of Special Population | Exposure |
|---|---|
| Patients with cardiovascular impairment | In the pivotal Phase 3, placebo-controlled clinical Studies 103/104, patients with history of risk factors for Torsades de Pointes, including familial long QT syndrome, hypokalaemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia and etc. were excluded. In addition, patients with QTc >450 msec were also excluded from the Phase 3 clinical studies. |
| Patients with a disease severity different from inclusion criteria in clinical trials | In the pivotal Phase 3, placebo-controlled clinical Studies 103/104, subjects with ppFEV$_1$ <40 at screening were excluded; however, the safety was evaluated in 81 subjects who had ppFEV$_1$ <40 at baseline. The pattern of AEs was similar across the subgroups by severity of lung disease. 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 these AEs compared to other subgroups. LUM/IVA was well tolerated even in this most severely compromised group.<br>In the open-label, Phase 3b Study 106, the safety of LUM/IVA treatment was evaluated for 24 weeks in 46 CF subjects aged 12 years and older who had advanced lung disease (e.g., ppFEV$_1$ <40). Overall, LUM/IVA was generally well tolerated in these subjects and the most common side effects were respiratory events (e.g., dyspnoea, chest discomfort, respiration abnormal), which occurred at a higher rate than observed in subjects with higher lung function in Studies 103/104. |
| Population with relevant different ethnic origins | 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, subgroup analysis of subjects of different ethnic origin is not possible. |
| **Other** | |
| Elderly patients | The oldest subject with CF who was treated with LUM/IVA in the Phase 3 studies was aged [redacted] years. Thus, the effect of LUM/IVA in elderly subjects has not been adequately evaluated. Given the current life expectancy of patients with CF, there are very few individuals with CF who live longer than 65 years. While this may change through continued improvements in care, the absence of an evaluation of the effects of LUM/IVA in elderly 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. Other common comorbid conditions associated with CF include CFLD, CFRD, osteoporosis and osteopenia, PI, depression, and cardiac disease. The clinical development programme included subjects with relevant comorbidities, and it is considered that all important subpopulation of patients who were homozygous for *F508del-CFTR* mutation have been exposed to the product in the clinical development programme. |
| Patients after organ transplant | It has been documented that patients with CF receive lung, heart lung, and liver transplants. Patients who received any organ transplant were excluded from clinical studies with LUM/IVA 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 have normal CFTR in the lungs, so they are not expected to benefit from LUM/IVA treatment with respect to their lung disease. In addition, LUM is an inducer of CYP3A and has the potential to interact with immunosuppressants commonly used in patients after organ transplant such as cyclosporine, tacrolimus, and sirolimus.<br>Therefore, the lack of clinical experience in this population is considered to be missing information. |
| Patients with CF who are heterozygous for *F508del-CFTR* mutation | Cohort 4 of Study 102 evaluated the safety and efficacy of LUM/IVA (56-day treatment) in 125 subjects who were heterozygous for the *F508del-CFTR* mutation on 1 allele plus a second allele with a mutation predicted to result in the lack of CFTR production or that is not responsive to IVA in vitro (62 received LUM/IVA and 63 received placebo). No statistically significant improvement in lung function was observed. The safety profile of LUM/IVA was comparable to that of the subjects who were homozygous. |

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC$_\tau$: area under the concentration versus time curve during the dosing interval; CF: cystic fibrosis; CFTR: CF transmembrane conductance regulator protein; CFLD: CF liver disease; CFRD: CF-related diabetes; $C_{max}$: maximum concentration; CYP: cytochrome P450; EMA: European Medicines Agency; *F508del*: CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein; GGT: gamma-glutamyl transferase; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: LUM in combination with IVA; M1-IVA: metabolite of IVA, hydroxymethyl-IVA; M6-IVA: metabolite of IVA, IVA carboxylate; PI: pancreatic insufficiency; PK: pharmacokinetics; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; QT: QT interval represents the duration of ventricular depolarisation and subsequent

| Type of Special Population | Exposure |
|---|---|

repolarisation; QTc: QT interval corrected for heart rate; ULN: upper limit of normal; US FDA: United States Food and Drug Administration

# SV Post-authorisation Experience

## SV.1 Post-authorisation Exposure

### *SV.1.1 Orkambi Post-authorisation Exposure*

#### Method Used to Calculate Exposure

Cumulative post-authorisation exposures to Orkambi include patients who initiated Orkambi treatment via commercial supply and were estimated using data at the time of distribution, not necessarily the time of usage. There may be a delay between the time a medication was distributed and the time a medication was used by a patient. The PY estimate is based on initial delivery and refill supply data using the number of days of treatment supplied for patients who initiated during the commercial supply period (varies from country to country) enumerated over all patients. Caution must be exercised when using post-authorisation exposure estimates to evaluate post-marketing reports. The exposure estimate includes patients who initiated Orkambi treatment via compassionate programmes.

Cumulatively since the International Birth Date (IBD; 02 July 2015), an estimated 24,1682 patients (representing 45,988 PY) have been exposed to Orkambi worldwide through commercial access, early access (e.g., named patient sales), or compassionate use (e.g., Expanded Access Programmes, Managed Access Programmes, Special Access Scheme [Australia], and Autorisation Temporaire d'Utilisation [France])(Table 7). Cumulative patient exposures for the US and Canada by age and sex are provided in Table 8 and Table 9, respectively.

**Table 7 Estimated Worldwide Cumulative Patient Exposure to Orkambi From Marketing Experience**

| Country | Patients | Person-years |
|---|---|---|
| EEA<br>UK<br>US | [redacted] | |
| Canada | | |
| Australia | | |
| Switzerland | | |
| Brazil | | |
| Israel | | |
| Russian Federation | | |
| ROW | 93 | 226.5 |
| Compassionate Use | 2,148 | 2,974.7 |
| **Total** | **24,168** | **45,988.0** |

**Table 7 Estimated Worldwide Cumulative Patient Exposure to Orkambi From Marketing Experience**

| Country | Patients | Person-years |
|---|---|---|

EEA: European Economic Area; ROW: rest of world; UK: United Kingdom; US: United States.
Notes:
UK includes England, Scotland, Wales, and Northern Ireland.
EEA includes Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Poland, Portugal, Spain, and Sweden.
ROW (e.g., named patient sales) includes Argentina, Cayman Islands, Colombia, Dominican Republic, Iceland, Kuwait, Norway, Oman, Saudi Arabia, South Africa, Turkey, and United Arab Emirates.
Compassionate Use includes Expanded Access Programs (US), Managed Access Programs (Austria, Belgium, Canada, Czech Republic, Denmark, Germany, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and United Kingdom), Special Access Scheme (Australia), and Autorisation Temporaire d'Utilisation (France).

**Table 8 Estimated Cumulative Patient Exposure to Orkambi From Marketing Experience in the US by Age and Sex**

| Age (years) | Female | | Male | | Unknown | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Patients | PY | Patients | PY | Patients | PY | Patients | PY |
| <2 | | | | | | | | |
| ≥2 to 5 | | | | | | | | |
| ≥6 to 11 | | | | | | | | |
| ≥12 to 17 | | | | | | | | |
| ≥18 | | | | | | | | |
| Unknown | | | | | | | | |
| **Total** | | | | | | | | |

PY: person-year; US: United States

**Table 9 Estimated Cumulative Patient Exposure to Orkambi From Marketing Experience in Canada by Age and Sex**

| Age (years) | Female | | Male | | Unknown | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Patients | PY | Patients | PY | Patients | PY | Patients | PY |
| <2 | | | | | | | | |
| ≥2 to 5 | | | | | | | | |
| ≥6 to 11 | | | | | | | | |
| ≥12 to 17 | | | | | | | | |
| ≥18 | | | | | | | | |
| Unknown | | | | | | | | |
| **Total** | | | | | | | | |

PY: person-year

# SVI Additional EU Requirements for Safety Specification

## Potential for Misuse for Illegal Purposes

No systematic examination of the abuse potential of LUM or LUM/IVA was performed in nonclinical and clinical studies. There is no information regarding the dependence potential in animals or humans. Evaluation of adverse events (AEs) did not reveal evidence of euphoria, sedation, or mood alteration. In addition, there were no clinically meaningful

central nervous system findings in the nonclinical or clinical studies of LUM. Therefore, LUM/IVA use is not expected to have the potential for misuse for illegal purposes.

LUM/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*

The ORKAMBI Summary of Product Characteristics (SmPC) describes the following adverse reactions identified from LUM/IVA clinical studies, as well as those from IVA monotherapy use, 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 are not expected to have any major impacts the benefit-risk profile of LUM/IVA.

| | | |
|---|---|---|
| Nasopharyngitis | Sputum increased | Dysmenorrhoea |
| Upper respiratory tract infection | Oropharyngeal pain | Metrorrhagia |
| Rhinitis | Sinus congestion | Breast mass |
| Headache | Rhinorrhoea | Menorrhagia |
| Dizziness | Pharyngeal erythema | Amenorrhoea |
| Ear pain | Abdominal pain | Polymenorrhoea |
| Ear discomfort | Abdominal pain upper | Breast inflammation |
| Tinnitus | Diarrhoea | Gynaecomastia |
| Tympanic membrane hyperaemia | Nausea | Nipple disorder |
| Vestibular disorder | Flatulence | Nipple pain |
| Ear congestion | Vomiting | Oligomenorrhoea |
| Nasal congestion | Rash | Bacteria in sputum |
| Productive cough | Menstruation irregular | Bronchospasm |

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

Descriptions of the important identified risk, 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 Identified Risk – Respiratory Events*

**Benefit-Risk Impact**

In the placebo-controlled Phase 3 studies, a higher incidence of respiratory event AEs was reported in the LUM/IVA treatment group compared to the placebo group during the first week of treatment; after the first week of treatment, the incidence of these events was balanced between both treatment groups. In a small number of patients, these events can be serious and may lead to study drug discontinuation; however, these events were not associated with any long-term sequelae. In addition, these events tend to occur more frequently in patients with lower pre-treatment $ppFEV_1$ (e.g., $ppFEV_1$ <40). The collective data suggest these events are associated with LUM/IVA treatment.

Overall, given the potential for these events to be serious or lead to study drug discontinuation, respiratory events is considered an important risk.

### *SVII.1.2.2 Important Potential Risk – Hepatobiliary Events*

**Benefit-Risk Impact**
In the Phase 3 placebo-controlled studies, the incidence of hepatobiliary events (AEs or laboratory elevations above threshold) was similar in the total LUM/IVA group and the placebo group, and the overall incidence and patterns were typical for the CF population. However, hepatobiliary event SAEs and marked transaminase elevations associated with increases in total bilirubin were only observed in the LUM/IVA group. Additionally, worsening of liver function manifested as hepatic encephalopathy occurred in a LUM/IVA-treated subject with a pre-existing history of both cirrhosis and portal hypertension. These events were confounded by complicated medical histories and alternative aetiologies, though a potential role of LUM/IVA cannot be excluded.

Overall, given the clinical significance of the events observed in the LUM/IVA-treated subjects, hepatobiliary events is considered an important risk; however, because of the presence of alternative aetiologies and/or other confounding factors, the role of LUM/IVA in these events is unclear, as such the risk is considered potential.

### *SVII.1.2.3 Important Potential Risk – Concomitant Use of LUM/IVA With Strong CYP3A Inhibitors or Inducers*

**Benefit-Risk Impact**
Strong CYP3A Inhibitors: The concurrent use of LUM/IVA with strong inhibitors has no impact on the LUM exposure. As IVA is a sensitive CYP3A substrate, the exposure of IVA can increase substantially when used in combination with a strong CYP3A inhibitor, in particular when the strong inhibitor is used before the CYP3A induction by LUM takes place.

Strong CYP3A Inducers: The concurrent use of LUM/IVA with strong inducers has no substantial impact on the overall LUM exposure. As IVA is a sensitive CYP3A substrate, the exposure of IVA can decrease substantially when used in combination with LUM and another strong CYP3A inducer.

Overall, changes in the metabolism of IVA may result in over-exposure or loss of efficacy when used with strong CYP3A inhibitors or inducers during LUM/IVA combination therapy. Therefore, concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers is considered an important potential risk.

### *SVII.1.2.4 Important Potential Risk – Concomitant Use of LUM/IVA With Sensitive CYP3A Substrates and CYP3A Substrates With a Narrow Therapeutic Index*

**Benefit-Risk Impact**
LUM is a strong inducer of CYP3A and concomitant use of LUM/IVA with certain CYP3A substrates may result in loss of efficacy of these substrate medications. Therefore, concomitant use of LUM/IVA with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index is considered an important potential risk.

### *SVII.1.2.5 Important Potential Risk - Cataracts*

**Benefit-Risk Impact**
Lens opacities (cataracts) were initially identified as a potential safety concern with IVA based on a nonclinical study in juvenile rats but was not observed in older animals or in longer duration nonclinical studies. Non-congenital cataracts have been reported from IVA monotherapy clinical studies and post-marketing surveillance. These reports consisted of subtle findings without any impact on vision, and the relationship of these events to IVA treatment is uncertain due to lack of baseline ophthalmological examinations (OE), the high

prevalence of background lens opacities, the subtlety of the ophthalmological findings, or other confounding risk factors.

Overall, the available evidence in humans does not support an association between IVA treatment and cataract development or progression; however, a contributing role cannot be completely excluded given the nonclinical findings in juvenile rats. Therefore, cataracts are considered an important potential risk.

#### *SVII.1.2.6 Important Potential Risk – Cardiac Arrhythmias*

**Benefit-Risk Impact**
In vitro studies showed that IVA inhibited the hERG channel. In the IVA 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. 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. While the finding was not considered to be adverse, there appeared to be a possible dose-related association with IVA. In the LUM/IVA repeat-dose toxicity study in dogs, noteworthy findings were limited to a higher incidence of non-adverse cardiovascular findings (PR prolongation, AV block, and SVPC runs) than previously noted in studies conducted with IVA alone.

Only a very small number of cardiac arrhythmia events have been observed in clinical studies with IVA or LUM/IVA and a similar incidence was observed with placebo-treated subjects. Taken together, the cardiac safety data from LUM/IVA and IVA monotherapy suggest that the nonclinical findings have no clinical relevance in humans.

Overall, cardiac arrhythmias is considered an important potential risk based on the nonclinical findings, which have not been confirmed in humans.

#### *SVII.1.2.7 Important Potential Risk – Off-label Use in Children Less Than 12 Years of Age or in Patients Who Are Not Homozygous for the F508del-CFTR Mutation*

**Benefit-Risk Impact**
The effects of LUM/IVA treatment have not been established in patients younger than 12 years of age or in patients who are not homozygous for the *F508del-CFTR* mutation; therefore, off-label use is considered an important potential risk.

#### *SVII.1.2.8 Missing Information – Use in Pregnant and Lactating Women*

**Benefit-Risk Impact**
Nonclinical studies demonstrated that both LUM and IVA are not teratogenic in rats and rabbits.

Both compounds are excreted into the milk of lactating female rats; therefore, excretion of LUM and of IVA into human milk is probable.

As a standard precautionary measure, pregnant and lactating women were excluded from clinical studies; therefore, safety data for LUM/IVA use in this population is considered to be missing information.

#### *SVII.1.2.9 Missing Information – Patients with $ppFEV_1$ <40*

**Benefit-Risk Impact**
Subjects with $ppFEV_1$ <40 at screening were excluded from the pivotal Phase 3 clinical studies (103/104); therefore, the experience of LUM/IVA treatment in this population is limited and considered to be missing information.

### *SVII.1.2.10 Missing Information – Long-term Safety*

**Benefit-Risk Impact**
The longest clinical study experience with LUM/IVA treatment is 48 weeks. As a chronic treatment, the long-term safety of LUM/IVA is considered missing information and further characterisation is needed.

### *SVII.1.2.11 Missing Information – Safety in Patients With Cardiac Disease*

**Benefit-Risk Impact**
In vitro studies showed that IVA inhibited the hERG channel. 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. 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. While the finding was not considered to be adverse, there appeared to be a possible dose-related association with IVA. In the LUM/IVA repeat-dose toxicity study in dogs, noteworthy findings were limited to a higher incidence of non-adverse cardiovascular findings (PR prolongation, AV block, and SVPC runs) than previously noted in studies conducted with IVA alone.

In clinical studies, patients with a history of significant cardiac disease were excluded and the experience of LUM/IVA treatment in this population is limited; therefore, the use in patients with cardiac disease is considered to be missing information.

### *SVII.1.2.12 Missing Information – Use in Patients With Organ Transplant*

**Benefit-Risk Impact**
In clinical studies, patients with a history of organ transplant were excluded and the experience of LUM/IVA treatment in this population is limited.

Additionally, LUM's strong induction effect on certain immunosuppressants (used after organ transplant) may result in reduced efficacy of these coadministered medications during LUM/IVA therapy.

Overall, LUM/IVA use in patients with organ transplant is considered missing information.

### *SVII.1.2.13 Missing Information – Effect of LUM/IVA on P-gp Substrates*

**Benefit-Risk Impact**
Based on in vitro results that showed P-gp inhibition and pregnane-X-receptor activation, LUM has the potential to both inhibit and induce P-gp. A clinical study with IVA monotherapy showed that IVA is a weak inhibitor of P-gp.

Overall, the relatively low potential for LUM/IVA therapy to alter the exposure of P-gp substrates, and the clinical significance of this effect, is considered missing information.

### *SVII.1.2.14 Missing Information Potential Off-target Activity of M6-IVA*

**Benefit-Risk Impact**
In LUM/IVA therapy, a higher dose of IVA (250 mg q12h) is used than in IVA monotherapy (150 mg q12h), and the exposure to M6-IVA (a major human metabolite of IVA) is higher in LUM/IVA therapy than that in IVA monotherapy.

As demonstrated in clinical studies, LUM/IVA therapy is well tolerated, and the higher exposure of M6-IVA does not appear to be a clinically relevant safety concern. However, the potential off-target activity (receptor binding and ion channel activity) of M6-IVA is currently unknown and considered missing information.

#### *SVII.1.2.15 Missing Information – Interaction Potential Between Transporters and LUM and/or IVA*

**Benefit-Risk Impact**
The potential for LUM or IVA to inhibit other transporter systems (e.g., BCRP, OAT1, OAT 3, OCT 1, and OCT 2) has not been fully characterised.

Because LUM is eliminated predominantly unchanged in the faeces, biliary secretion by transporters may be involved; however, it is currently unknown if LUM is a substrate for BCRP and MRP 2.

Therefore, the interaction potential between transporters and LUM and/or IVA is considered missing information.

#### *SVII.1.2.16 Missing Information – Potential Environmental Risk*

**Benefit-Risk Impact**
The environmental risk assessments for LUM and IVA are currently incomplete and do not allow a definitive conclusion on the potential risks of LUM and IVA to the environment. Thus, the potential environmental risk is considered missing information.

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

#### *SVII.2.1 Reclassified to an Important Identified Risk – Hepatobiliary Events*

Orkambi Periodic Safety Update Report (PSUR) 2 (EMEA/H/C/PSUSA/10455/201611) presented a post-marketing report of [redacted] leading to death in a patient with [redacted] as well as a comprehensive analysis of cumulative hepatobiliary events in patients with advanced liver disease. Based on Pharmacovigilance and Risk Assessment Committee (PRAC) and Committee for Medicinal Products for Human Use (CHMP) recommendation during the assessment of Orkambi PSUR 2, the important potential risk of "Hepatobiliary events" was reclassified as an important identified risk in EU Risk Management Plan (RMP) Version 3.3.

#### *SVII.2.2 Added Important Identified Risk – Blood Pressure Increase*

In EU RMP Version 2.2, Blood pressure (BP) increase was added as an important identified risk based on findings from the Phase 3, 24-week, placebo-controlled Studies 103/104, in which an increase in BP was observed in LUM/IVA-treated subjects 12 years of age and older.

#### *SVII.2.3 Updated Important Potential Risk – 'Off-label Use in Children Less Than 12 Years of Age or in Patients Who Are Not Homozygous for the F508del-CFTR Mutation' to 'Off-label Use in Children Less Than 2 Years of Age or in Patients Who Are Not Homozygous for the F508del-CFTR Mutation'*

On 08 January 2018, the line extension submission for Orkambi use among children aged 6 to 11 years was approved. The details of the relevant risks and missing information (Section SVII) were updated accordingly, including a revision to the criterion for the important potential risk of Off-label use from "patients less than 12 years of age" to "patients less than 6 years of age" in EU RMP Version 3.6.

On 15 January 2019, the line extension submission (EMEA/H/C/003954/X/0034/G) for Orkambi use among children aged 2 to 5 years was approved. The details of the relevant risks and missing information were updated accordingly, including a revision to the criterion for

the important potential risk of Off-label use from "patients less than 6 years of age" to "patients less than 2 years of age" in EU RMP Version 5.4.

### *SVII.2.4 Added Missing Information – Clinical Relevance of Heart Rate Decreased*

In EU RMP Version 2.2, the "Clinical relevance of heart rate decrease" was added as missing information based on findings from Phase 3 Studies 103/104, in which a small, transient decrease in heart rate was observed in subjects treated with LUM/IVA. The maximum overall decrease in heart rate observed was approximately 6 beats per minute at 4 to 6 hours postdose, and associated AEs occurred in very few subjects and at similar incidences between the LUM/IVA and placebo groups. Further evaluation is needed to determine if there is any clinical relevance to this effect.

### *SVII.2.5 Updated Missing Information – Clinical Relevance of Interaction Potential Between Transporters and LUM and/or IVA*

Nonclinical studies assessing the interaction potential between transporters and LUM and/or IVA showed that LUM and IVA have the potential to inhibit some transporter systems. Base on PRAC recommendation following review of these results, the missing information of "Interaction potential between transporters and LUM and/or IVA" was updated to "Clinical relevance of interaction potential between transporters and LUM and/or IVA" in EU RMP Version 2.4.

### *SVII.2.6 Removed Missing Information - Potential Off-target Activity of M6-IVA*

In EU RMP Version 2.5, the final results from in vitro studies to evaluate potential off-target activity for M6-IVA were added. The results showed no off-target activities for M6-IVA, suggesting no clinical relevance; therefore, the missing information of "Potential off-target activity of M6-IVA" was removed.

### *SVII.2.7 Removed Missing Information - Potential Environmental Risk*

In EU RMP Version 6.0, the results from environmental risk assessments of LUM and IVA were added. The results showed that both LUM and IVA were unlikely to represent a risk to the aquatic or terrestrial environment; therefore, the missing information of "Potential environmental risk" was removed.

### *SVII.2.8 Removed Important Potential Risk – Off-label use in children less than 2 years of age or in patients who are not homozygous for F508del-CFTR mutation*

The important potential risk of "Off-label use in children less than 2 years of age or in patients who are not homozygous for *F508del-CFTR* mutation" is removed in EU-RMP Version 9.0 based on the cumulative evaluation of this risk conducted for the 5-year renewal procedure for Orkambi. Since the initial marketing authorization of Orkambi when the approved indication was limited, CFTR modulators are now approved for treatment of CF in greater than 90% of the patient population. As such, the corresponding patient population for potential off-label use has also been significantly reduced. Review of the post-marketing experience and the LTSS confirms off-label use is limited, and has not identified any trend, pattern, or new safety concerns. In addition, the safety profile of Orkambi was demonstrated to be similar across age groups during indication expansion. As such, the cumulative experience does not support the maintenance of this topic as an important potential risk in the RMP Summary of Safety Concerns.

### *SVII.2.9 Removed Missing Information – Patients with ppFEV$_1$<40*

The missing information of "Patients with ppFEV$_1$ <40" is removed in EU-RMP Version 9.0 based on the cumulative evaluation conducted for the 5-year renewal procedure for Orkambi.

The cumulative data from clinical studies, the LTSS, published literature, and post-marketing experience in subjects and patients with $ppFEV_1$ <40 demonstrated that LUM/IVA treatment is well tolerated in patients with $ppFEV_1$ <40 resulting in clinical meaningful and durable treatment benefit, comparable to patients with $ppFEV_1$ ≥40, without any specific new safety concerns. Overall, the safety in this population is sufficiently characterized and adequately addressed in the SmPC and CCDS. As such, the overall evidence does not support the maintenance of use in "Patients with $ppFEV_1$ <40" as missing information in the RMP Summary of Safety Concerns.

Respiratory events reported in this population will be discussed within the important identified risk of "Respiratory events".

### *SVII.2.10 Removed Missing Information – Safety in Patients with Cardiac Diseases*

The missing information of "Safety in Patients with Cardiac Diseases" is removed in EU-RMP Version 9.0 based on the cumulative evaluation of risks conducted for the 5-year renewal procedure for Orkambi. Overall, Orkambi use among patients with a history of cardiac disease is limited due to the rarity of the comorbidity in this population. The safety in this population was observed to be consistent with the overall CF population and no specific safety concerns were identified for this subpopulation through the cumulative post-marketing evidence. As such, the overall evidence does not support the maintenance of "Safety in Patients with Cardiac Disease" as missing information in the RMP Summary of Safety Concerns.

### *SVII.2.11 Removed Missing Information – Clinical Relevance of Heart Rate Decrease*

The missing information of "Clinical Relevance of Heart Rate Decrease" is removed in EU-RMP Version 9.0 based on the cumulative evaluation of risks conducted for the 5-year renewal procedure for Orkambi. Overall, the cumulative post-marketing experience with Orkambi use was consistent with previous clinical experience, which describes LUM/IVA's PDeffect to decrease heart rate as generally asymptomatic with limited clinical relevance. As such, the overall evidence does not support the maintenance of "Clinical Relevance of Heart Rate Decreased" as missing information in the RMP Summary of Safety Concerns.

### *SVII.2.12 Removed Missing Information – Effect of LUM/IVA on P-gp Substrates*

The missing information of "Effect of LUM/IVA on P-gp Substrates" is removed in EU-RMP Version 9.0 based on the cumulative evaluation of risks conducted for the 5-year renewal procedure for Orkambi. Overall, the cumulative post-marketing experience has demonstrated limited use of P-gp substrates in Orkambi-treated patients, without reports of DDIs. The cumulative data are supportive that the relatively low DDI potential between Orkambi and P-gp substrates is unlikely to be clinically relevant and does not support the maintenance of the "Effect of LUM/IVA on P-gp substrates" as missing information in the RMP Summary of Safety Concerns.

### *SVII.2.13 Removed Missing Information – Clinical Relevance of Interaction Potential Between Transporters and LUM and/or IVA*

The missing information of "Clinical Relevance of Interaction Potential Between Transporters and LUM and/or IVA" is removed in EU-RMP Version 9.0 based on the cumulative evaluation of risks conducted for the 5-year renewal procedure for Orkambi. Overall, the post-marketing experience has not suggested any safety concerns associated with this risk. The cumulative data are supportive that the relatively low DDI potential between Orkambi and transporters is unlikely to be clinically relevant. As such, the cumulative evidence does not support of the "Clinical Relevance of Interaction Potential between

Transporters and LUM and/or IVA" as missing information in the RMP Summary of Safety Concerns.

### *SVII.2.14 Removed Important Potential Risk – Concomitant Use of LUM/IVA with Strong CYP3A Inhibitors or Inducers*

The important potential risk of "Concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers" was removed because there are no additional pharmacovigilance or risk minimisation activities associated with this potential risk. Furthermore, a search of the global safety database for patients with reported adverse events within the MedDRA high level term (HLT) of Interactions identified relatively few patients in the post-marketing setting, and the majority of cases involved drug interactions that are 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.2.15 Removed Important Potential Risk – Concomitant Use of LUM/IVA with Sensitive CYP3A Substrates and CYP3A Substrates With a Narrow Therapeutic Index*

The important potential risk of "Concomitant use of LUM/IVA with Sensitive CYP3A Substrates and CYP3A Substrates With a Narrow Therapeutic Index" was removed because there are no additional pharmacovigilance or risk minimisation activities associated with this potential risk. Furthermore, a search of the global safety database for patients with reported adverse events within the MedDRA HLT of Interactions identified relatively few patients in the post-marketing setting, and the majority of cases involved drugs interactions already noted in the SmPC. These reports of suspected DDIs were generally consistent with the known DDI profile of Orkambi, which is clearly described in the warnings and precautions in the Orkambi product labelling.

### *SVII.2.16 Removed Missing Information – Long-term Safety*

The missing information of "Long-term Safety" was removed based on favorable long-term safety outcomes in up to 120 weeks of treatment in completed clinical trials and 5 years of registry data in the completed Post-authorisation Safety Study (PASS; Study 108).

LUM/IVA was generally safe and well-tolerated for up to 96 weeks of treatment (cumulatively up to 120 weeks) in subjects 6 years and older in Study 110 and subjects 2 through 5 years of age in Study 116. The safety outcomes following extended LUM/IVA treatment were generally consistent with underlying CF disease and the established safety profile of LUM/IVA treatment. No new safety concerns were observed.

The results of the Orkambi PASS (Study 108) support the overall favourable benefit-risk profile of Orkambi. Annual analyses of 5 years of data from the US CF registry and 1 year of data from the UK CF registry demonstrated no new safety concerns but showed lower risks for outcomes of death, organ transplant, pulmonary exacerbation, and hospitalisation in Orkambi-treated versus Comparator patients. Overall, the results of the annual analyses performed from 2016 through 2020 are consistent with the safety profile of Orkambi.

### *SVII.2.17 Removed Important Identified Risk – Blood Pressure Increase*

Following the completion of the PASS, no further additional pharmacovigilance activities are ongoing or proposed and there are no additional risk minimisation measures associated with any of the safety concerns. Therefore, PRAC requested to remove the important identified risk of "Blood pressure increase" from the safety concerns.

### *SVII.2.18 Removed Important Identified Risk – Hepatobiliary Events*

Following the completion of the PASS, no further additional pharmacovigilance activities are ongoing or proposed and there are no additional risk minimisation measures associated with any of the safety concerns. Therefore, PRAC requested to remove the important identified risk of "Hepatobiliary Events" from the safety concerns.

### *SVII.2.19 Removed Important Potential Risk – Cardiac Arrhythmias*

Following the completion of the PASS, no further additional pharmacovigilance activities are ongoing or proposed and there are no additional risk minimisation measures associated with any of the safety concerns. Therefore, PRAC requested to remove the important identified risk of "Cardiac Arrhythmias" from the safety concerns.

## 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 Identified Risk – Respiratory Events*

**Potential mechanisms**
The mechanism for the respiratory events within the first few days of treatment is not presently known. However, it is postulated to be due to a transient, self-limiting, off-target bronchoconstriction. Ex vivo safety pharmacology studies suggest a potential for LUM at concentrations up to the clinical $C_{max}$ had no statistically significant effect on airway narrowing and only a minimal effect noted on the contractility of airway tissues. This effect is likely an overestimate due to high plasma protein binding and subsequent low free $C_{max}$ of LUM observed clinically.

**Evidence source(s) and strength of evidence**
In the placebo-controlled Phase 3 studies, a higher incidence of respiratory event AEs was reported in the LUM/IVA treatment group compared to the placebo group during the first week of treatment; after the first week of treatment, the incidence of these events was balanced between both treatment groups.

Similar observations were also seen in other clinical studies, including open-label extension studies, studies in subjects with various disease severities, and across different age groups.

**Characterisation of the risk**
For the clinical study data analyses, the group term "Respiratory events" encompasses the following Preferred Terms: Chest discomfort, Dyspnoea, Respiration abnormal, Asthma, Bronchial hyperreactivity, Bronchospasm, and Wheezing.

<u>Studies 103/104</u>
In the pooled, placebo-controlled, Phase 3 Studies 103/104 in subjects aged 12 years and older, respiratory events were reported in 26.3% in the total LUM/IVA group compared with 17.0% in the placebo group. Among the respiratory events, dyspnoea, and respiration abnormal were the most commonly reported events:

- Incidence of dyspnoea: 14.0% in the total LUM/IVA group and 7.8% in the placebo group
- Incidence of respiration abnormal: 9.8% in the total LUM/IVA group and 5.9% in the placebo group

The incidence of respiratory events was similar across the 2 active treatment groups (LUM 600 mg qd/IVA 250 mg q12h group; LUM 400 mg q12h/IVA 250 mg q12h group).

Most of the respiratory events occurred during the first week of LUM/IVA treatment initiation. After the first week of treatment, the incidence of these events was balanced between the total LUM/IVA and placebo groups. The median time-to-onset of the respiratory events was 2 days in the total LUM/IVA group compared to 24 days in the placebo group. The median duration of these events was 6 days for the total LUM/IVA treatment group and 8 days for the placebo group.

Most respiratory event AEs were non-serious, mild to moderate in severity, and resolved with continued LUM/IVA treatment. Four subjects (0.5%) in the total LUM/IVA group had respiratory SAEs and 5 subjects (0.7%) in the total LUM/IVA group discontinued treatment due to these events.

In subjects with lower pre-treatment $ppFEV_1$, the respiratory events occurred more frequently, however, the nature and severity of these events appeared to be comparable to these in subjects with higher pre-treatment $ppFEV_1$.

Study 105

During an additional 96 weeks of LUM/IVA treatment in Study 105, 32.6% of subjects overall had respiratory events. The respiratory event AEs were consistent with the data from Studies 103/104 and were mostly mild or moderate in severity. In Study 105, 0.8% of subjects overall had a serious respiratory event AE. The incidence of treatment discontinuation (2.3%) or interruption (1.3%) due to these events remained low, was similar across all 4 treatment groups, and showed no consistent trends. Consistent with data from Studies 103/104, respiratory events in Study 105 remained more common in subjects with lower pre-treatment $ppFEV_1$.

In Study 105, the median time-to-onset of first respiratory event AEs was substantially shorter in LUM/IVA-naïve subjects (i.e., 14 days [LUM 600 mg qd/IVA 250 mg q12h] and 2 days [LUM 400 mg q12h/IVA 250 mg q12h]) than in subjects previously exposed to the study drug (i.e., 162 days [LUM 600 mg qd/IVA 250 mg q12h] and 107 days [LUM 400 mg q12h/IVA 250 mg q12h]). The later time-to-onset of the respiratory events in subjects previously treated with LUM/IVA suggested these may be a reflection of the background events. The median event duration was similar across both dose groups and ranged from 13 days (LUM 600 mg qd/IVA 250 mg q12h) to 15 days (LUM 400 mg q12h/IVA 250 mg q12h).

Study 106

In the Phase 3, open-label Study 106, 46 subjects with advanced lung disease (e.g., $ppFEV_1$ <40) aged 12 years and older were treated with LUM/IVA for 24 weeks. The overall incidence of respiratory events was 65.2%. In the subgroup of subjects who initiated LUM/IVA at 1 tablet of LUM 200 mg/IVA 125 mg q12h the incidence was 55.6%, and in those who initiated at 2 tablets of LUM 200 mg/IVA 125 mg q12h the incidence was 71.4%.

One subject (2.2%) had a respiratory SAE. Respiratory events led to treatment discontinuation in 3 subjects (6.5%) and dose reduction in 3 subjects (6.5%). The median time-to-onset of the respiratory events was 1 day, and the median duration of these events was 9 days.

Studies 011 Part B and 109

In subjects 6 to 11 years of age, respiratory event data were obtained from open-label Study 011 Part B and placebo-controlled Study 109.

In Study 011 Part B, a total of 4 (6.9%) subjects had respiratory events.

In Study 109, the incidence of respiratory events was 18.4% in LUM/IVA-treated subjects and 12.9% in placebo subjects. A decline in $ppFEV_1$ at initiation of therapy was observed during serial postdose spirometry assessments. The absolute change from predose at 4 to 6 hours postdose on Day 1 was -7.7. The postdose decline was largely attenuated by Day 15 (1.3 at 4 to 6 hours postdose) and resolved by Week 16.

During both Studies 011 Part B and 109, all respiratory events were non-serious and either mild or moderate in severity. Only 1 (1.0%) subject in Study 109 taking LUM/IVA had respiratory events that led to interruption and discontinuation of treatment.

Study 110
During an additional 96 weeks of LUM/IVA treatment among subjects aged 6 years and older in Study 110 Treatment Period 1, a total of 44 (18.4%) subjects had respiratory events, all of which were mild or moderate in severity. Asthma and dyspnoea each occurred in 10 (4.2%) subjects, chest discomfort in 5 (2.1%) subjects, respiration abnormal in 14 (5.9%) subjects, and wheezing in 12 (5.0%) subjects. None of the events were SAEs.

Only 1 (0.4%) subject had respiratory AEs of [redacted] leading to LUM/IVA discontinuation, and 1 subject had an AE of dyspnoea that led to LUM/IVA interruption. Overall, results were similar to outcomes in Studies 109/011B. The data suggested a lower incidence of respiratory events in this age group compared to subjects 12 years of age and older.

Study 115 Part B
In subjects 2 to 5 years of age, respiratory events were obtained from open-label, Phase 3 Study 115 Part B. A total of 6 (10.0%) subjects had respiratory event AEs, all of which were mild or moderate in severity, non-serious, and did not lead to LUM/IVA discontinuation or interruption. The median time to onset was 9.0 days, and the mean event duration was 6.1 days.

Study 116
During an additional 96 weeks of LUM/IVA treatment among subjects aged 2 years and older in Study 116, a total of 5 (8.8%) subjects had respiratory events, all of which were mild or moderate in severity. None of the events were SAEs or led to treatment discontinuation or interruption. The median time-to-onset of the first adverse event of special interest (AESI) was 72.0 days, and the median duration of events was 11.0 days.

Overall, the exposure-adjusted event rate for respiratory events was lower in Study 116 compared to parent Study 115.

Study 122 Part B
In subjects 1 to less than 2 years of age, respiratory events were obtained from open-label Phase 3 Study 122 Part B. One (2.2%) subject had a respiratory event AE of [redacted] that occurred on Day [redacted] and was assessed by the investigator to be non-serious and moderate in severity. The evening dose of study drug was interrupted, and the event resolved with [redacted]. Study drug was resumed on Day [redacted], and the event did not recur.

Study 124
During an additional 96 weeks of treatment in subjects 1 to less than 2 years at enrollment that rolled over from Study 122, 3 (5.8%) subjects had respiratory events. All events were non-serious and mild in severity, and none led to treatment interruption or discontinuation.

Post-marketing Data
The post-marketing data suggest the rate of serious respiratory events and the rate of respiratory events leading to treatment discontinuation may be higher than those observed in clinical studies, particularly in patients with $ppFEV_1$ <40.

**Risk factors and risk groups**
General risk factors for respiratory events may include underlying CF and its associated sequelae (e.g., obstructive lung disease, bronchial hyperreactivity, bronchiectasis, acute and chronic lung infections, haemoptysis, pneumothorax, and respiratory failure). Overall, respiratory events occur more frequently and tend to be more severe or lead to discontinuation in patients with lower $ppFEV_1$.

**Preventability**
The off-target bronchoconstriction can be largely prevented by long-acting bronchodilators and reversed by short-acting bronchodilators.

**Impact on the benefit-risk balance of the product**
The impact on individual patients may vary. These events can be serious and may lead to LUM/IVA treatment discontinuation, particularly in patients with $ppFEV_1$ <40. In considering the significant unmet medical need for CF treatments that address the underlying cause of the disease, and the nature of the events (i.e., mostly mild/moderate, short-lived, resolved without treatment discontinuation), these respiratory events appear to be mainly a tolerability issue rather than a significant safety concern impacting the risk-benefit profile of LUM/IVA treatment.

Respiratory events are described in the prescribing information, along with a recommendation for additional monitoring in patients with $ppFEV_1$ <40 during initiation of treatment. Further characterisation via the pharmacovigilance plan and the routine risk minimisation measures will be conducted to assess the appropriateness of the measures in place.

**Public health impact**
No impact on public health is anticipated.

### *SVII.3.1.2 Important Potential Risk – Cataracts*

**Potential mechanisms**
Lens opacities (cataracts) were initially identified as a potential safety concern with IVA based on a nonclinical study in juvenile rats. Although the aetiology 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 hyaloids vessels.

**Evidence source(s) and strength of evidence**
Lens opacities (cataracts) were seen during nonclinical studies in juvenile rats but were not observed in older animals or in longer duration studies. Non-congenital cataracts have been reported from IVA monotherapy and LUM/IVA clinical studies and post-marketing surveillance, but the relationship of these events to treatment is uncertain.

**Characterisation of the risk**
Overall, a small number of cataract events have been reported from both the LUM/IVA and IVA clinical studies and post-marketing surveillance. The majority of these reports involved subtle findings and were not visually significant. No AEs of cataracts were reported in

Studies 115 and 116 in subjects 2 to 5 years of age. No AEs of cataracts were reported in Study 122 Part B in subjects 1 to less than 2 years of age. Overall, the relationship of these events to LUM/IVA or IVA treatment is uncertain due to lack of baseline OE, the high prevalence of background lens opacities, the subtlety of the ophthalmological findings, or other confounding risk factors (e.g., corticosteroid use, history of uncontrolled diabetes).

Additionally, final data from ocular safety Study 770-115 showed a lack of cataract progression in patients treated with IVA monotherapy based on the Lens Opacity Classification System, Version III (LOCS III) grading.

**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.[77]

**Preventability**
The preventability of cataracts is unknown.

**Impact on the benefit-risk balance of the product**
Overall, the available evidence in humans does not support an association between treatment and cataract development or progression, although a contributing role cannot be completely excluded given the nonclinical findings. Given the subtlety of the clinical cataract findings, this potential risk is not expected to have a significant impact on the benefit-risk balance for LUM/IVA.

The potential effect on cataracts is described in the prescribing information, including a recommendation for baseline and follow-up OE is in paediatric patients. This risk is closely monitored to assess the appropriateness of the current pharmacovigilance plan and risk minimisation measures.

**Public health impact**
No public health impact is expected.

### *SVII.3.2 Presentation of the Missing Information*

#### *SVII.3.2.1 Missing Information – Use in Pregnant and Lactating Women*

**Evidence source**
Nonclinical studies demonstrated that both LUM and IVA are not teratogenic in rats and rabbits. Both LUM and IVA were found to be non-teratogenic during nonclinical studies in rats and rabbits.

Both compounds are excreted into the milk of lactating female rats; therefore, excretion of LUM and of IVA into human milk is probable.

As a standard precautionary measure, pregnant and lactating women were excluded from clinical studies.

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

#### *SVII.3.2.2 Missing Information – Use in Patients With Organ Transplant*

**Evidence source**
In clinical studies, patients with a history of organ transplant were excluded and the experience of LUM/IVA treatment in this population is limited.

Additionally, LUM's strong induction effect on certain immunosuppressants (used after organ transplant) may result in reduced efficacy of these coadministered medications during LUM/IVA therapy.

**Population in need of further characterization**
The safety of LUM/IVA use in patients with organ transplant will be further characterised in the post-marketing setting.

## SVIII Summary of Safety Concerns

| | |
|---|---|
| **Important identified risks** | •Respiratory events |
| **Important potential risks** | •Cataracts |
| **Missing information** | •Use in pregnant and lactating women<br>•Use in patients with organ transplant |

# 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
- Depression-related Adverse Event Information Request Form

## III.2 Additional Pharmacovigilance Activities

Not applicable

## III.3 Summary Table of Additional Pharmacovigilance Activities

| **Planned and Ongoing Post-authorisation Studies in the Pharmacovigilance Plan** | | | | |
|---|---|---|---|---|
| **Study/Status** | **Summary of Objectives** | **Safety Concerns Addressed** | **Milestones** | **Due Dates** |
| **Category 1 – Imposed mandatory additional PV activities that are Conditions of the MA (key to benefit risk)** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional PV activities that 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: marketing authorization; PV: pharmacovigilance

# PART IV Plans for Post-authorisation Efficacy Studies

| Study/Status | Summary of Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Efficacy studies that are conditions of the MA** | | | | |
| Post-Authorisation Efficacy Study (PAES) (Study Number 809-128)<br><br>*Ongoing* | Long-term effectiveness study.<br>To compare disease progression among children with CF homozygous for *F508del-CFTR* and are aged 2 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort. | Benefits of early initiation of Orkambi in CF patients aged 2 to 5 years who are homozygous for *F508del-CFTR*. | Protocol Submission | June 2020 |
| | | | Interim Analysis | December 2022 |
| | | | Final Study Report | December 2025 |
| | | Benefits of early initiation of Orkambi in CF patients aged 1 to less than 2 years who are homozygous for *F508del-CFTR* | Final Study Report | December 2025 |
| **Efficacy studies that are Specific Obligations in the context of a conditional MA or a MA under exceptional circumstances** | | | | |
| None | | | | |

CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; *F508del*: CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein; MA: marketing authorisation; PAES: Post-Authorisation Efficacy Study

Note: The PAES was expanded to include patients who initiate Orkambi at 1 to <2 years of age.

# PART V Risk Minimisation Measures

## V.1 Routine Risk Minimisation Measures

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| **Respiratory Events** | **Routine risk communication:**<br>SmPC Sections 4.4 and 4.8<br>PL Sections 2 and 4 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>Recommendation for additional monitoring in patients with ppFEV$_1$ <40 is included in SmPC Section 4.4 and in PL Section 2 |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Cataracts** | **Routine risk communication:**<br>SmPC Sections 4.4 and 5.3<br>PL Section 2 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>Recommendations for baseline and follow-up ophthalmologic examinations in paediatric patients are included in SmPC Section 4.4 and in PL Section 2. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Use in pregnant and lactating women** | **Routine risk communication:**<br>SmPC Sections 4.6 and 5.3<br>PL Section 2 |

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>Advice for use during pregnancy or during breastfeeding is included in SmPC Section 4.6 and PL Section 2. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Use in patients with organ transplant** | **Routine risk communication:**<br>SmPC Sections 4.4 and 4.5<br>PL Section 2 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>Advice that Orkambi use in this population is not recommended is provided in SmPC Section 4.4 and PL Section 2.<br>A list of list of immunosuppressants (used after organ transplant) with which concomitant use of Orkambi is not recommended is provided in SmPC Section 4.5 and PL Section 2. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |

PL: Patient Leaflet; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SmPC: Summary of Product Characteristics

## V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities, as described in Part V.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 |
|---|---|---|
| **Respiratory Events** | **Routine risk minimisation measure:**<br>SmPC Section 4.4 and PL Section 2 where advice is given for additional monitoring in patients with $ppFEV_1$ <40.<br>SmPC Section 4.8<br>PL Section 4<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>None |
| **Cataracts** | **Routine risk minimisation measure:**<br>SmPC Section 4.4 and PL Section 2 where advice is given on baseline and follow-up ophthalmological examinations in paediatric patients.<br>SmPC Section 5.3<br>Prescription only<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>None |
| **Use in pregnant and lactating women** | **Routine risk minimisation measure:**<br>SmPC Section 4.6 and PL Section 2 where advice is given on the use of Orkambi during pregnancy and breastfeeding.<br>SmPC Section 5.3<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Pregnancy follow-up form<br><br>**Additional PV activities:**<br>None |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Use in patients with organ transplant** | **Routine risk minimisation measure:**<br>SmPC Section 4.4 and PL Section 2 where advice is given that Orkambi use in this population is not recommended.<br>SmPC Section 4.5 and PL Section 2 provide a list of immunosuppressants (used after organ transplant) with which concomitant use of Orkambi is not recommended.<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>None |

PL: Package Leaflet; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; PV: pharmacovigilance; SmPC: Summary of Product Characteristics

# PART VI Summary of the RMP

## Summary of Risk Management Plan for ORKAMBI (lumacaftor/ivacaftor)

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

ORKAMBI's SmPC and its package leaflet (PL) give essential information to healthcare professionals and patients on how ORKAMBI should be used.

This summary of the RMP for ORKAMBI 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 ORKAMBI's RMP.

## I. The medicine and what it is used for

ORKAMBI tablets are authorised for the treatment of CF in patients aged 6 years and older who are homozygous for the *F508del-CFTR* mutation. ORKAMBI granules are authorised for the indicated treatment of children with CF aged 1 to 5 years who are homozygous for the *F508del-CFTR* mutation. See SmPC for the full indication.

Further information about the evaluation of ORKAMBI's benefits can be found in ORKAMBI'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/orkambi.

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

Important risks of ORKAMBI, together with measures to minimise such risks and the proposed studies for learning more about ORKAMBI'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 PL 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 the case of ORKAMBI, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 ORKAMBI is not yet available, it is listed under 'missing information' below.

### *II.A List of important risks and missing information*

Important risks of ORKAMBI 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 ORKAMBI. 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** | •Respiratory events |
| **Important potential risks** | •Cataracts |
| **Missing information** | •Use in pregnant and lactating women<br>•Use in patients with organ transplant |

### *II.B Summary of important risks*

The safety information in the proposed Product Information is aligned to the reference medicinal product.

| **Respiratory events** | |
|---|---|
| Evidence for linking the risk to the medicine | Some respiratory events (e.g., chest tightness and shortness of breath) were observed with Orkambi treatment. In two 24-week, placebo-controlled studies, most of these events were mild or moderate in severity and did not require discontinuation of Orkambi treatment. These events mostly occurred during the first week of treatment and resolved within a few days without a need to change the dose of Orkambi.<br>Patients who were treated with Orkambi for up to 120 weeks did not show any worsening of these events over time.<br>Respiratory events can be serious and can sometimes lead to stopping Orkambi treatment, particularly in patients with poor lung function.<br>During a study in patients aged 6 through 11 years, a decrease in lung function test results was observed within hours of taking Orkambi. This decline in lung function mostly resolved after 2 weeks of treatment. |
| Risk factors and risk groups | General risk factors for respiratory events may include underlying CF and its associated pulmonary manifestations.<br>Overall, respiratory events occur more frequently and tend to be more severe or lead to discontinuation in patients with lower ppFEV$_1$. |

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.4 and PL Section 2 where advice is given for additional monitoring in patients with ppFEV$_1$ <40.<br>SmPC Section 4.8<br>PL Section 4<br>Prescription only<br>**Additional risk minimisation measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |
| **Cataracts** | |
| 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 the developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 2 years of age and older.<br>In the IVA and Orkambi programmes, there have been some reports of non-congenital (not present since birth or the first year of life) lens abnormalities in patients. The majority of the reported events involved small findings and did not affect vision. The relationship of these events to IVA monotherapy and Orkambi therapy is uncertain because of the presence of other possible causes. |
| Risk factors and risk groups | Risk factors for cataracts include aging, trauma to the eye, ultraviolet light and radiation exposure, diabetes mellitus, intraocular (inside the eye) inflammation, and systemic or topical corticosteroid use. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.4 and PL Section 2 where advice is given on ophthalmological examinations in paediatric patients.<br>SmPC Section 5.3<br>Prescription only<br>**Additional risk minimisation measures:**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |
| **Use in pregnant and lactating women** | |
| Risk minimisation measures | SmPC Section 4.6 and PL Section 2 where advice is given on the use of Orkambi during pregnancy and breastfeeding.<br>SmPC Section 5.3<br>Prescription only |
| Additional pharmacovigilance activities | None |
| **Use in patients with organ transplant** | |
| Risk minimisation measures | SmPC Section 4.4 and PL Section 2 where advice is given that Orkambi use in this population is not recommended.<br>SmPC Section 4.5 and PL Section 2 provide a list of immunosuppressants (used after organ transplant) with which concomitant use of Orkambi is not recommended.<br>Prescription only |
| Additional pharmacovigilance activities | None |

CF: cystic fibrosis; IVA: ivacaftor; PL: package leaflet; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SmPC: Summary of Product Characteristics.

## *II.C Post-authorisation development plan*

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

The following studies are conditions of the marketing authorisation:

**Study Name and Title:** The Post-Authorisation Efficacy study (PAES) is an observational, registry-based study to evaluate the benefits of early initiation of LUM/IVA in CF patients aged 2 to 5 years who are homozygous for *F508del-CFTR.*

Note: The PAES was expanded to evaluate patients who initiate LUM/IVA at 1 to less than 2 years of age.

**Rationale and Study Objectives:**

The objective of this study is to evaluate benefits of early initiation of LUM/IVA

***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)*<br>☐ Hospitalization Date of Admission: Discharge:<br>☐ Important Medical Event<br>☐ Life-threatening<br>☐ Permanent Disability<br>☐ Congenital Anomaly<br>☐ Death Date of Death: | | | **Event Outcome**<br>☐ Recovered / Resolved<br>☐ Recovering / Resolving<br>☐ Recovered / Resolved w Sequelae<br>☐ Not Recovered / Not Resolved (Ongoing)<br>☐ Fatal<br>☐ 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 ___**<br>**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)*<br>☐ Hospitalization Date of Admission: Discharge:<br>☐ Important Medical Event<br>☐ Life-threatening<br>☐ Permanent Disability<br>☐ Congenital Anomaly<br>☐ Death Date of Death: | | | **Event Outcome**<br>☐ Recovered / Resolved<br>☐ Recovering / Resolving<br>☐ Recovered / Resolved w Sequelae<br>☐ Not Recovered / Not Resolved (Ongoing)<br>☐ Fatal<br>☐ 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.*

VERTEX

Global Patient Safety
50 Northern Avenue
Boston, MA 02210

**ORKAMBI (lumacaftor/ivacaftor)**

**Depression-related Adverse Event (AE): Information Request**

| | |
|---|---|
| **To:** | |
| **Fax / Email:** | |
| **From:** | Vertex Global Patient Safety |
| **Date:** | [today] |
| **Re:** | Subject: [patient_id] / Patient Initials: [patient_initials]<br>Protocol: [study_id]<br>AER number: [case_num] |
| **Reported AE(s):** | Reported Term(s): [VRTX_event_desc_rpt] |

We have received a report of an Adverse Event (AE) for the above referenced patient. **Global Patient Safety** would appreciate responses to the queries listed below as soon as possible to help us further analyze the event. This information will be important to us in our endeavor of providing safe and effective medicines to our patients.

**AE Information Request:**

1. Please provide the following details for the event of [event term]:
   a. Description (e.g., symptoms, manifestations):

   b. Onset Date:

   c. Outcome (with resolution date, if available):

2. Does the patient have any prior history of depression (e.g., depressed mood, suicidal/self-injurious ideation, decreased interest)? If so, please provide details.

3. Does the patient have any history of substance use (including illicit drugs or alcohol)? If so, please provide details.

4. Is there a family history of depression? If so, please provide details.

5. Were there any possible psychosocial stressors before or during the depression-related event (e.g., financial stress, death of family/friend, academic or employment stress/loss, relational stress)? If so, please provide details.

Information Request for Depression-related Adverse Events Version 2.0 (May 2021)

6. Please list all of the medications the patient was taking during the event, including details (e.g., name of the medication, start and stop dates, dose, frequency, and indication for each medication [as applicable]).

7. Was the patient taking an antidepressant medication before the event? If so, please provide details (e.g., name of the medication, start and stop dates, dose, frequency, and indication for each medication [as applicable]).

8. Was there any change to this antidepressant medication just before or during the event? If so, did depression symptoms change? Please provide details.

9. Was treatment provided for the event? If so, did depression symptoms improve? Please provide details.

10. Does this event meet serious criteria? Please circle the applicable criteria:

Hospitalization  Important Medical Event  Life-threatening  Permanent Disability  Congenital Abnormality  Death

11. Please provide the causality assessment with [study drug / Marketed Name]. Please check one:

Related:_____  Not related:_____

12. Was any action taken with [study drug / Marketed Name] as a result of the event? If so, did depression symptoms change as a result of this action taken with [study drug / Marketed Name]?

13. [Update per clinical trial vs. postmarketing] Please provide the following details regarding therapy with [study drug / Vertex Marketed Product Name]:

    a. Feeder trial: VX__-_____: Start _____ Stop _____

    b. Current trial: VX__-_____: Start _____ Stop _____Ongoing? Yes ____No ____

    c. Lot #_____ Expiration date_____

Completed by: _____
(Printed Name)

Information Request for Depression-related Adverse Events  Version 2.0 (May 2021)

Signature: _____

Date: _____

Investigator: _____
(Printed Name)

Signature: _____

Date: _____

**Send all additional information to:**

| | |
|---|---|
| **Vertex** Global Patient Safety | Email: [redacted] (Preferred Choice)<br>Fax :<br>Telephone: [redacted] |

Any questions, please call Vertex Global Patient Safety at [redacted]

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

Not applicable.

# REFERENCES

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