**Module 1.8.2**

# EU RISK MANAGEMENT PLAN

For KAFTRIO (elexacaftor in combination with tezacaftor and ivacaftor)

**RMP Version Number:** 10.1
**Data lock for this RMP:** 20 April 2025
**Date of final sign off:** 13 June 2025

**Rationale for submitting an updated RMP:** The RMP was updated to align with the conclusion of 96 weeks of treatment in Study VX20-445-112 (Study 112). Study 112 is an open-label extension study evaluating the long-term safety and efficacy of ELX/TEZ/IVA treatment in CF subjects 2 years of age and older. Subjects who participated in Study VX20-445-111 Part B were eligible to enroll in Study 112. Study 112 was included in the RMP as a post-marketing commitment and this RMP was updated to reflect completion of the RMP milestone, i.e., the completion of 96 weeks of treatment.

**Summary of significant changes in this RMP:** The RMP was updated to reflect the completion of 96 weeks of ELX/TEZ/IVA treatment in Study 112. The details of relevant important safety concerns were updated to align with the findings from 96 weeks of treatment in Study 112. The pharmacovigilance plan and annexes were also updated to reflect the completion of this milestone.

## Other RMP versions under evaluation

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

## Current approved RMP

| RMP version number | Date of opinion | Approved with procedure |
|---|---|---|
| 10.0 | 04 April 2025 (EC decision) | EMEA/H/C/005269/WS2551/0043 |

**QPPV Name:** Jan Petráček, MD, MSc, DIC

**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 |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUCτ | area under the concentration versus time curve during a dosing interval |
| BCRP | breast cancer resistance protein |
| BP | blood pressure |
| CF | cystic fibrosis |
| CFRD | CF-related diabetes |
| *CFTR* | CF transmembrane conductance regulator gene |
| CFTR | CF transmembrane conductance regulator protein |
| Cmax | maximum observed concentration |
| CT | computed tomography |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| ECFSPR | European CF Society Patient Registry |
| ECG | electrocardiogram |
| EEA | European Economic Area |
| ELX | elexacaftor |
| ELX/TEZ/IVA | elexacaftor/tezacaftor/ivacaftor |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |
| F508del | an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein |
| *F/F* | homozygous for the *F508del* mutation in the *CFTR* gene |
| *F/*Gating | heterozygous for the *F508del* mutation in the *CFTR* gene with a gating mutation |
| *F/*MF | heterozygous for the *F508del* mutation in the *CFTR* gene with a minimal function mutation |
| *F/*RF | heterozygous for the *F508del* mutation in the *CFTR* gene with a residual function mutation |
| IV | intravenous |
| IVA | ivacaftor |
| LFT | liver function test |
| N | number of subjects |
| n/a | not available |
| NOAEL | no-observed-adverse-effect level |
| OAT | organic anion transporter |
| OATP | organic anion-transporting polypeptide |
| OCT | organic cation transporter |
| PASS | post-authorisation safety study |
| PD | pharmacodynamic(s) |
| P-gp | permeability glycoprotein |
| PK | pharmacokinetic(s) |
| PL | Package Leaflet |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PV | Pharmacovigilance |
| PY | person-year, patient year |
| q12h | every 12 hours |
| Q3 | Quarter 3 |
| qd | 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 |
| RMP | risk management plan |
| SAE | serious adverse event |

| Abbreviation | Definition |
|---|---|
| SmPC | Summary of Product Characteristics |
| TC | triple combination |
| TEZ | tezacaftor |
| TEZ/IVA | TEZ in combination with IVA |
| TNF | Tumour necrosis factor |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| UV | ultraviolet |

# PART I Product(s) Overview

| | |
|---|---|
| **Active substance(s)** | **KAFTRIO (elexacaftor/tezacaftor/ivacaftor [ELX/TEZ/IVA])** |
| **Pharmacotherapeutic group(s) (ATC Code)** | Other respiratory system products (R07AX32) |
| **Market Authorisation Applicant** | Vertex Pharmaceuticals (Ireland) Limited |
| **Medicinal products to which this RMP refers** | ELX/TEZ/IVA |
| **Invented name(s) in the European Economic Area (EEA)** | KAFTRIO |
| **Market authorisation procedure** | centralised |
| **Brief description of the product** | ELX is N-(1,3-dimethyl-1*H*-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1*H*-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide.<br>TEZ is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide<br>IVA is N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide |
| | ELX is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector that facilitates the cellular processing and trafficking of multiple mutant forms of CFTR (including *F508del-CFTR*) to increase the amount of functional CFTR protein delivered to the correct location in the cell surface, resulting in increased chloride transport. The effect of TEZ (another CFTR corrector) administered in combination with ELX is additive to the effect of ELX alone.<br>IVA is a CFTR potentiator that increases the channel open probability (or gating) of CFTR at the cell surface to enhance chloride transport. For IVA to function, CFTR protein must be present at the cell surface. IVA can potentiate the CFTR protein delivered to the cell surface by ELX and TEZ, leading to a further enhancement of chloride transport than achieved with dual therapy alone. |
| **Hyperlink to the Product Information** | (Current) Summary of Product Characteristics for KAFTRIO |
| **Indication(s) in the EEA** | **Current (if applicable):** KAFTRIO is indicated in a combination regimen with IVA tablets or granules for the treatment of CF in patients aged 2 years and older who have at least one non-class I mutation in the *CFTR* gene. |
| | **Proposed (if applicable):** Not applicable |
| **Dosage in the EEA** | **Current (if applicable): For patients aged ≥12 years and older, and patients aged 6 to <12 years weighing ≥30 kg:** In a combination regimen with IVA 150 mg tablets, the recommended dose is 2 KAFTRIO tablets (each containing ELX 100 mg/ TEZ 50 mg/IVA 75 mg) taken in the morning and 1 IVA 150 mg tablet taken in the evening, approximately 12 hours apart.<br><br>**For patients aged 6 to <12 years weighing <30 kg:** In a combination regimen with IVA 75 mg tablets, the recommended dose is 2 KAFTRIO tablets (each containing ELX 50 mg/ TEZ 25 mg/IVA 37.5 mg) taken in the morning and 1 IVA 75 mg tablet taken in the evening, approximately 12 hours apart.<br><br>**For patients aged 2 to <6 years weighing ≥14 kg**: In a combination regimen with IVA 75 mg granules, the recommended dose is 1 KAFTRIO granule sachet (each containing ELX 100 mg + TEZ 50 mg + IVA 75 mg)<br><br>**For patients aged 2 to <6 years weighing 10 to <14 kg**: In a combination regimen with IVA 59.5 mg granules, the recommended dose is 1 KAFTRIO granule sachet (each containing ELX 80 mg + TEZ 40 mg + IVA 60 mg) |
| | **Proposed (if applicable):** Not applicable |
| **Pharmaceutical form(s) and strengths** | **Current (if applicable): ELX 100 mg/TEZ 50 mg/IVA 75 mg tablets:** Each film coated tablet contains ELX 100 mg/ TEZ 50 mg/IVA 75 mg as a fixed dose combination tablet, which is orange, capsule-shaped, and debossed with "T100" on one side and plain on the other (dimensions: 7.85 mm × 15.47 mm).<br><br>**ELX 50 mg/TEZ 25 mg/IVA 37.5 mg tablets:** Each film coated tablet contains ELX 50 mg/ TEZ 25 mg/IVA 37.5 mg as a fixed dose combination tablet, which |

| | |
|---|---|
| | is light orange, capsule-shaped, and debossed with "T50" on one side and plain on the other (dimensions: 6.4 mm × 12.2 mm).<br><br>**ELX 100 mg/TEZ 50 mg/IVA 75 mg granules**: Each sachet of film coated oral granules contains ELX 100 mg/TEZ 50 mg/IVA 75 mg as fixed-dose combination oral granules, which are white to off-white, sweetened, unflavoured granules approximately 2 mm in diameter.<br><br>**ELX 80 mg/TEZ 40 mg/IVA 60 mg granules**: Each sachet of film coated oral granules contains ELX 80 mg/TEZ 40 mg/IVA 60 mg as fixed-dose combination oral granules, which are white to off-white, sweetened, unflavoured granules approximately 2 mm in diameter. |
| | **Proposed (if applicable):** Not applicable |
| **Is/will the product be subject to additional monitoring in the EU** | Yes |

# PART II Safety Specification

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

## CYSTIC FIBROSIS

The target population for elexacaftor in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA) is patients with cystic fibrosis (CF) who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data.

### SI.1 Incidence

Europe: The incidence of CF in Europe varies markedly, ranging from 1:1,353 in Ireland to 1:25,000 in Finland.[1] Annual cumulative incidence estimates reported for other European countries include: 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, France 1 in 4,348, Germany 1 in 3,300, Hungary 1 in 4,000, 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, and Sweden 1 in 5,600. [1]

UK: In the UK, the incidence of CF is 1 in 2,381.[1]

US: In the US, among white persons, CF occurs in approximately 1 in 3,000 to 4,000 live births. In other races and ethnicities, CF occurs less commonly, including approximately 1 in 4,000 to 10,000 Latin Americans, 1 in 15,000 to 20,000 African Americans, and even less commonly in Asian Americans.[2] In 2017, 880 new cases of CF were diagnosed in the US.[3]

Canada: In Canada, based on CF patient registry data in 2000, approximately 1 in 3,600 children were born with CF.[4] In Canada in 2017, 115 patients were newly diagnosed with CF, including 66 patients diagnosed through newborn screening programmes.[5]

Australia: Approximately 1 in 3,700 children in Australia were born with CF in 2017.[6]

### SI.2 Prevalence

#### General CF Population

CF affects more than 70,000 individuals worldwide.[7]

Europe: A survey of standards of care in Europe conducted from 2007 to 2009, EuroCare CF, estimated there were 39,897 patients with CF who were treated in 32 European countries.[8] According to another survey performed by Orphanet, the prevalence of CF from European data is 0.74 per 10,000.[9]

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

US: In the US in 2017, there were 29,887 patients with CF in the US CF Foundation patient registry; an overall prevalence of 0.9 per 10,000 people.[3, 10]

Canada: In Canada in 2017, there were 4,309 patients with CF in the Canadian CF Registry; an overall prevalence of 1.18 per 10,000 people.[5, 10]

Australia: In Australia in 2017, there were 3,151 patients with CF in the Australian CF Data Registry; an overall prevalence of 1.3 per 10,000 people.[6, 11]

**Target Population**

Europe: Based on the 2017 report from the European CF Society Patient Registry (ECFSPR) that included data on 48,204 patients with CF from 35 countries in the EU, 81.1% of the patients with available genotype data and who were seen in 2017 had at least one *F508del* allele.[12]

US: Based on the 2017 report from the US CF Foundation patient registry that included data on 29,887 patients with CF, 98.6% of the patients in the registry had been genotyped. Of the patients with available genotype data, 85.8% had at least one *F508del* allele.[3]

Canada: Based on the 2017 report from the Canadian CF Registry that included data on 4,309 patients with CF, 98.3% of the patients in the registry had at least 1 CF mutation genotyped. Of those with available genotype data, 89.1% had at least one *F508del* allele.[5]

Australia: Based on the 2017 report from the Australian CF registry that included data on 3,151 patients with CF, 94.1% of the patients in the registry had been genotyped. Of those with available genotype data, 89.2% had at least one *F508del* allele.[6]

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

**Risk Factors for the disease**

CF is an autosomal recessive genetic disorder. To have CF, a person must inherit 2 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 approximately 2, 4, and 2 months, as reported by the CF registries in UK[13], Ireland[14], and France[15], respectively. Across 35 countries that contributed data to ECFSPR in 2017, the median age at diagnosis was 4.0 months.[12]

Similarly, in the US, the median age at diagnosis was 3 months according to a 2017 registry report.[3]

In Canada, newborn screening is performed in all provinces (Quebec added CF testing to their newborn screening in 2018). In 2017, the majority (59.9%) of individuals with CF were diagnosed by 1 year of age.[5]

**Age distribution among prevalent patients**

Of the 48,204 CF patients from 35 countries in the ECFSPR (including non-EU member states) in 2017 and with a patient encounter in that year, the mean age was 20.8 years and of the total population 51.3% were older than 18 years of age.[12]

In the US, 53.5% of all CF patients were adults 18 years or older based on the 2017 annual registry report.[3] Despite the gains in median survival, the age distribution remains markedly skewed to the young. While the age of US CF patients ranged from birth to a maximum age of 87.7 years, the mean age was 21.7 years in 2017.[3]

In Canada in 2017, CF patients ranged from birth to more than 70 years old, with the median age being reported as 22.8 years and 60.9% of patients with CF were 18 years or older, with 15.2% being over 40 years of age, and 0.5% over the age of 70.[5]

**Sex**

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

Among CF children in Europe, a male preponderance exists at birth and persists and is reflected at all ages.[19] Based on the ECFSPR report for 2017, 52.6% out of 48,204 CF patients from 35 countries were males.[12] In the 2018 annual report for the UK, 53% of patients were males.[13]

In the US 2017 annual registry report, 51.6% of all CF patients were males.[3]

In Canada, based on 2017 annual patient registry report, 53.9% of patients with CF were males.[5]

**Race / ethnic origin**

CF affects all racial and ethnic groups, but is more common among Caucasians.[20] Among CF patients in the US, 93.6% were Caucasians, 4.6% African Americans, and 3.6% other races, with 8.7% being identified as Hispanic (any race) (races are not mutually exclusive as recorded in US CF Foundation).[3]

## SI.4 Main Existing Treatment Options

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

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

| Comorbidity | Treatment Options |
|---|---|
| CF lung disease | • Airway hydration (hypertonic saline nebulisation)<br>• Mucolytics (dornase alfa)<br>• Oral antibiotics (amoxicillin clavulanate, ciprofloxacin, azithromycin, clarithromycin)<br>• Inhaled antibiotics (tobramycin, aztreonam, colistin)<br>• IV antibiotics (ceftazidime, meropenem, piperacillin-tazobactam, tobramycin, amikacin)<br>• Bronchodilators (albuterol, salmeterol)<br>• Oxygen<br>• Inhaled corticosteroids (budesonide, fluticasone)<br>• Systemic corticosteroids (prednisolone, prednisone) |
| CF liver disease | • Oral bile acid therapy (ursodeoxycholic acid) |
| CFRD | • Insulin |

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

| | |
|---|---|
| CF-related osteoporosis and osteopenia | • Vitamin D and calcium supplementation |
| Pancreatic insufficiency / Malnutrition | • 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) |
| CF arthropathy | • Systemic corticosteroids (prednisolone, prednisone)<br>• Methotrexate<br>• TNF blockers, TNF receptor blockers |
| Anxiety and depression | • Anxiolytics<br>• Antidepressants |
| Cardiac disease | • Digitalis and tolazoline hydrochloride have been reported as treatments for heart failure secondary to CF; however, no clear benefit of these treatments has been identified and they remain controversial.[21] |

CF: cystic fibrosis; CFRD: CF-related diabetes; IV: intravenous; TNF: tumor necrosis factor

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

### Mortality

EuroCare CF 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.[8] A female survival disadvantage exists.[12]

A patient with CF born in the last 2 decades of the 20th century (in an economically developed nation) is now expected to have a greater-than-50% chance of survival to 40 years of age.[19] In an international cohort of 366 patients with CF aged 40 years or older from Canada, UK, US, and Italy, the estimated annual mortality rate was 3.4%.[18]

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

| Country, Year | Median age at death (years) | Median predicted survival (years) | Annual Mortality rate |
|---|---|---|---|
| UK, 2018[13] | 32.0 | 47.3 | 1.3% |
| Ireland, 2017[14] | 32.0 | 45.7 | 1.2% |
| France, 2016[15] | 28.0 | n/a | 0.8% |
| Germany, 2016[22] | 33.0 | n/a | 1.1% |
| US, 2017[3] | 30.6 | 43.6 | 1.3% |
| Canada, 2017[5] | 33.6 | 52.3 | 1.0% |
| Australia, 2017[6] | 35.6 | n/a | 0.6% |

n/a: not available

### Morbidity

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

## SI.6 Important Comorbidities

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

### *SI.6.1 Cystic Fibrosis Lung Disease*

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

In 2017, 46.4% of US CF patients had at least one positive culture for *P aeruginosa* as characterised by the Leeds criteria, with 28.6% being categorised as having chronic infection and 17.8% as intermittent infection, and for methicillin-resistant *S aureus, Burkholderia cepacia complex, S aureus*, the prevalence is 25.9%, 2.5%, and 70.7%, respectively.[3] Pulmonary infection is the most pronounced clinical issue and the progressive pulmonary dysfunction is the main prognostic factor for patients with CF.

According to the 2017 report from the CF Registry of Ireland, 34.6% of patients had at least one pulmonary exacerbation requiring intravenous (IV) antibiotics; 24.4% of children (<18 years, n=130) and 42.3% of adults (≥18 years; n=298).[14] 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.[23-25] 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.[3]

CF lung disease is characterised by progressive airway obstruction as measured by percent predicted forced expiratory volume in 1 second ($ppFEV_1$). 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.[26] Taken together, these values reflect progressive lung disease from the earliest age at which lung function is measurable.

Lung disease is the most serious complication of CF, causing the majority of mortality in patients with CF. In the US, 62.9% of all 2017 deaths were due to respiratory/cardiorespiratory and 16.1% were transplant-related.[3] Of all the 380 deaths which occurred in 2017, 47.6% occurred in people who were *F508del* homozygotes.[3]

### *SI.6.2 Cystic Fibrosis Liver Disease*

While there is no standard, universally accepted definition of what constitutes CF liver disease, 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:[27-30]

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

As defined by a combination of any 2 signs (i.e., hepatomegaly/splenomegaly, increased liver function tests (LFTs), and/or ultrasound), the cumulative incidence of CF liver disease based on long-term follow-up was 18% in the US, 27% in Italy, and 28% in Israel.[31-33]

The incidence rate of CF liver disease 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.[32, 34]

Liver function test abnormalities

Liver abnormalities are very common among CF infants with up to 53% having elevated LFTs by 3 years of age.[35] In 2 large CF patient registries in UK (2018) and Australia (2017), prevalence of abnormal LFTs in the overall CF population (all ages) was reported at 9.0% and 10.2%, respectively.[6, 13]

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

If followed for 5 to 10 years, about 35% to 50% of CF patients would have LFT elevations on at least 1 occasion,[32, 34] with up to 93% of patients with LFT abnormalities over 20 years of follow-up.[37]

Of note, while transient or even persistent LFT increases are frequent in CF, they have a low sensitivity and specificity in predicting clinically significant CF liver disease. For instance, in 1 study among patients with abnormal liver enzyme testing, 25% went on to develop CF liver disease during follow-up (mean of 8 years).[31]

Clinically significant liver disease

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

The literature suggests that up to 10% of patients with CF develop cirrhosis, with most of these patients having signs of portal hypertension.[32, 35, 38] In the US patient registry in 2017, prevalence of cirrhosis in the CF population was 3.1%. In the UK patient registry in 2018, prevalence in the CF population for cirrhosis without portal hypertension was 0.7% and prevalence of cirrhosis with portal hypertension was 1.1%.[3,11]

Two prospective studies[32, 34] reported sufficient data to estimate the incidence rates of clinically significant liver disease. Using the reported case counts and person-time from these 2 studies, the rates were estimated at:

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

Liver disease, including liver failure, remains an important non-pulmonary cause of death, accounting for about 3.4% of overall CF mortality in the US.[3]

In Ireland, among all deaths recorded between 2002 and 2014, 4.0% were caused by liver disease.[39]

During 7-year follow-up of 36 children with CF liver disease, 3 (8%) patients died from liver failure and 1 (3%) patient received a liver transplant. Another 3 (8%) patients with CF liver disease died from pulmonary failure. Overall, the mortality at 7 years was 19.4% in the cohort of patients with CF liver disease.[40]

### *SI.6.3 Cystic Fibrosis-Related Diabetes*

Three 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%[41], and 2 cohorts from Georgia and Minnesota, US, reported 31.2% and 33% CFRD, respectively.[42, 43] The prevalence increased with age, reaching 31% to 50% in adults.[41-43]

In the 2 largest CF patient registries (US and UK), prevalence of CFRD in the US in 2017 was 18.5% (overall) and in the UK in 2018 was 26.6% (ages ≥10 years old).[3, 13] CFRD increases with age, with prevalence of 31.0% among those 18 years and older versus 5.3% among those younger than 18 years in US (2017)[3], and 31.1% among those ≥16 years of age versus 7.4% among those 10 to 15 years of age in UK (2018).[13]

The annual incidence of CFRD was estimated at 3.8% in a Danish cohort[44], 3.5% in a British cohort[45], and 2.7% in a US cohort.[43] 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.[44]

It is believed that CFRD causes a more rapid decline in pulmonary function and nutrition status, particularly in female patients, compared to CF patients without CFRD. There is also evidence that CFRD is associated with increased mortality.[46]

Data from the UK CF Registry showed the age-adjusted mortality rate among patient with CFRD was 4.2 (95% CI: 3.4 to 5.1) per 100 PY, while the rate in patients with CF but without CFRD was only 1.5 (95% CI: 1.3 to 1.7) per 100 PY.[47] 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.[48]

### *SI.6.4 Cystic Fibrosis-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.[49] Low bone mineral density value was found even with daily calcium dosages of 1200 or 1500 mg.[50-53]

A meta-analysis of osteoporosis, osteopenia, and vertebral and non-vertebral fractures among adults with CF reported pooled prevalence of 23.5%, 38%, 14%, and 19.7%, respectively.[54] In 2017, about 3.8% and 10.4% of people with CF in the US were reported to have osteoporosis and osteopenia, respectively.[3] In the UK in 2018, 4.7% and 10.3% of all CF patients had osteoporosis and osteopenia, respectively.[13]

Fractures are very common in patients with CF, and often more than 1 fracture occurs during the life of a patient with CF.[49] Studies estimated that fracture rate was increased 2fold in women aged 16 to 34 years and in men aged 25 to 45 years, as compared to the general population.[50]

### *SI.6.5 Pancreatic Insufficiency / Malnutrition*

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

Two studies independently found that among cohorts of patients with CF in Canada and the US, 87% had pancreatic insufficiency.[56, 57] In a cohort of patients with CF over 40 years of age in the UK, 82% had pancreatic insufficiency as identified in clinical notes.[58]

### *SI.6.6 Anxiety and Depression*

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

In the US in 2017, a clinical diagnosis of depression was reported in 15.5% and anxiety disorder was reported in 12.5% of all CF patients.[3] In 2017, depression or anxiety was diagnosed in 12.6% of CF patients in Canada.[5]

In the CF population, the prevalence of depression increases in adolescents and in young adults and remains high through older ages. In the US in 2017, depression was reported in 3.6% of patients <18 years of age and 26.8% of patients ≥18 years of age; anxiety disorder was reported in 4.1% of patients ≥18 years of age and 20.6% of patients ≥18 years of age.[3] In Canada in 2017, depression or anxiety was clinically diagnosed in 4.7% of patients <18 years of age and in 17.6% of patients ≥18 years of age.[5]

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

Within this same study by Quittner et al., the sample of CF patients included 1,286 adolescents (aged 12 to 17 years) and 4,739 adults (aged ≥18 years). Depending on age and the screening tool used, rates of depression varied across countries, ranging from

5 to 19% in adolescents and 13 to 29% in adults. Furthermore, 4% of the adolescent patients with CF and 10% of the adult patients with CF reported currently taking a psychiatric medication for depression/anxiety, while 6% of the adolescent CF patients and 8% of the adult CF patients reported currently receiving psychotherapy.[59]

In 2015, the CF Foundation and the European CF Society published recommendations for annual screening and treatment of depression and anxiety in all individuals with CF who are 12 years of age and older. As a steady increase is being observed in the number of patients screened for anxiety and depression, the prevalence of diagnosed anxiety and depression is also increasing over time.[3]

#### *SI.6.7 Cardiac Disease*

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

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

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

## SII Nonclinical Part of the Safety Specification

Nonclinical studies were conducted to evaluate the pharmacologic activity of ELX and to characterise its pharmacokinetic (PK) and toxicity profile (Module 2.4). TEZ and IVA were previously evaluated in similar sets of studies to support the clinical development of Symdeko/Symkevi and Kalydeco, respectively. Several studies involving the co-administration of combination therapy with ELX, TEZ, and IVA were also conducted.

### SII.1 Toxicity

The nonclinical safety programme supports the chronic administration of the triple combination (TC) regimen of ELX/TEZ/IVA in humans at the intended clinical doses.

In repeat-dose toxicity studies in rats, key findings included gastric erosions and/or ulcerations, hypocellularity of the bone marrow, seminiferous tubule degeneration and/or testicular atrophy, persistent corpus luteum in the ovaries, and reduced fertility. There was at least a 2× exposure margin (based on no-observed-adverse-effect level [NOAEL]) for these rat-specific findings. Similar findings were not observed in the 28-day and 39-week dog studies even though markedly higher systemic exposures were achieved (19× exposure margin at NOAEL for 39-week study). The Phase 3 clinical data suggest that these nonclinical findings do not translate to humans; therefore, based on this and the established

exposure margins, these findings are considered rat-specific and are not anticipated to present a risk to humans at the therapeutic dose (ELX 200 mg/day).

Combination repeat-dose toxicity studies up to 3 months in duration in rats and 28 days in duration in dogs did not result in any new or synergistic toxicities following co-administration with ELX, TEZ, and IVA. Based on these findings, there are no anticipated risks associated to humans with co-administration of the TC therapy.

ELX was not teratogenic in rat and rabbit embryo-foetal development studies. No adverse findings were identified in the rat pre- and post-natal development and juvenile toxicity studies. Therefore, there is minimal human risk of developmental toxicity with ELX.

Placental transfer of $^{14}$C-ELX, $^{14}$C-TEZ, and $^{14}$C-IVA associated radioactivity was observed in pregnant rats. After oral administration to lactating female rats, $^{14}$C-ELX, $^{14}$C-TEZ, and $^{14}$C-IVA were excreted in the milk.

ELX was non-genotoxic, did not cause the formation of preneoplastic or other proliferative lesions in any tissue in the 28-day, 3-month, and chronic toxicity studies in rats and dogs, and was noncarcinogenic in a 26week Tg.rasH2 transgenic mouse carcinogenicity assay. In the 2year oral carcinogenicity study in rats evaluating the carcinogenic potential of ELX, administration of ELX up to 10 mg/kg/day by oral gavage in male and female rats for up to 93 weeks did not results in neoplastic or non-neoplastic findings.

Similarly, TEZ and IVA were non-genotoxic, non-carcinogenic in a 26-week Tg.rasH2 transgenic mouse carcinogenicity assay (TEZ), non-carcinogenic in a 2-year carcinogenicity bioassay in mice (IVA), and non-carcinogenic in a 2-year bioassay in rats (TEZ and IVA). Based on the available data, the overall carcinogenic risk associated with the TC regimen is low.

### SII.2 Safety Pharmacology

Results from safety pharmacology studies and secondary pharmacodynamic (PD) screening evaluating ELX, TEZ, and IVA suggest a high degree of selectivity and a low potential for adverse biological or physiological effects when ELX, TEZ, and IVA are administered in combination. Furthermore, in a thorough QT interval corrected for heart rate (QTc) study, there were no clinically important trends attributable to ELX dosing identified in vital sign assessments, blood pressure (BP), heart rate, and no effects were noted in ECG data, including QTc prolongation or arrhythmias.

### SII.3 Pharmacokinetics

ELX, TEZ, and IVA absorption, distribution, metabolism, and excretion and PK properties have been adequately characterised to support the registration of the ELX, TEZ, and IVA TC therapy.

ELX was orally bioavailable in all species tested. Systemic exposures to ELX, TEZ, and IVA in combination studies in rats and dogs were similar to the exposures observed when these compounds were dosed individually. Adequate exposures of ELX, TEZ, and IVA were achieved for nonclinical safety evaluation.

After oral administration of $^{14}$C-ELX, $^{14}$C-TEZ, or $^{14}$C-IVA, radioactivity was rapidly distributed across most tissues in rats. Protein binding is high for ELX (>98.9%), TEZ (≥98.0%), and IVA (>99.3%) in mouse, rat, dog, monkey, and human plasma, and is similar across species.

ELX metabolism was similar between nonclinical species and humans. M23-445 is a major circulating metabolite observed for ELX in humans. M1-TEZ and M5-TEZ are major circulating metabolites of TEZ in humans and rats. M2-TEZ is a major disproportionate circulating metabolite of TEZ in humans. M1-IVA and M6-IVA are the major circulating metabolites of IVA in all species studied. All major metabolites of ELX, TEZ, and IVA have been adequately qualified in nonclinical toxicity studies.

ELX, TEZ, and IVA are substrates of CYP3A. Concomitant use of CYP3A inducers or inhibitors may affect their exposures. ELX, TEZ, IVA and their metabolites are predicted to have low potential to cause drug-drug interactions (DDIs) via CYP inhibition except that IVA may inhibit CYP2C9.

Based on in vitro results, ELX and M23-445 have a low potential to inhibit efflux transporter permeability glycoprotein (P-gp), but they have the potential to inhibit hepatic uptake transporters organic anion-transporting polypeptides (OATP) 1B1 and OATP1B3 at the clinical daily dose of 200 mg. TEZ and its major metabolites have a low potential to inhibit major efflux (P-gp, breast cancer resistance protein [BCRP]), hepatic uptake (OATP1B1, OATP1B3, organic cation transporter [OCT] 1), and renal uptake (OCT2, organic anion transporter [OAT] 1 and OAT3) transporters. IVA has been shown to be a weak P-gp inhibitor in a clinical DDI study with digoxin. IVA has the potential to inhibit efflux transporter BCRP. IVA is not expected to inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3.

Overall, based on in vitro transporter inhibition studies, ELX/TEZ/IVA TC therapy has the potential to alter PK of co-medications or endogenous substrates (such as bilirubin) that are eliminated via OATP1B1/1B3 hepatic uptake transport. The mild isolated increases in serum bilirubin observed in clinical studies with TC therapy are consistent with OATP1B1/1B3 transporter inhibition.

### SII.4 Other Toxicity-Related Information or Data

The photosafety of ELX was evaluated and determined not to have phototoxicity potential based on nonclinical study results in rats.

## SIII Clinical Trial Exposure

Cumulatively, a total of 3,487 subjects have been exposed to at least 1 dose of ELX, either as monotherapy or combination therapy in clinical studies (Table 1): 3,240 were subjects with CF (5,644.53 person-years [PY] exposure) and 247 were healthy subjects (4.61 PY). Additionally, 432 subjects have been exposed to at least 1 dose of placebo (378 were CF subjects and 54 were healthy subjects), and a total of 271 subjects (all CF subjects) have been exposed to an active comparator (e.g., TEZ/IVA alone).

Exposure in the ELX development clinical studies was calculated using patient years (PY). As shown in Table 1, subjects were exposed to ELX treatment during clinical studies for approximately 5649.14 PY, in comparison to 184.56 PY for the placebo subjects and 68.78 PY for the active comparator subjects.

The cumulative subject exposure by duration, age, sex, and race are provided in Table 2, Table 3, Table 4, and Table 5, respectively. Overall, of the 3,487 subjects exposed to ELX treatment, the [redacted] were aged ≥18 years, and [redacted] There were [redacted] subjects than [redacted] subjects on ELX treatment.

**Table 1 Summary of Exposure in the ELX Clinical Development Program by Dose**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| **Dose** | **N = 301** | **Total Exposure (PY)** | **N = 3258** | **Total Exposure (PY)** | **N = 3559** | **Total Exposure (PY)** |
| **Total** | **301** | **6.62** | **3258** | **5895.86** | **3559** | **5902.48** |
| **Active (combination and monotherapy)** | **247** | **4.61** | **3240** | **5644.53** | **3487** | **5649.14** |
| **Combination (ELX TC)** | **146** | **2.38** | **3240** | **5644.53** | **3386** | **5646.91** |
| ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h | 34 | 0.73 | 3037 | 5216.19 | 3071 | 5216.92 |
| ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h | 22 | 0.65 | 231 | 397.56 | 253 | 398.21 |
| ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg qAM + 59.5 mg qPM | 0 | -- | 44 | 25.04 | 44 | 25.04 |
| ELX 60 mg qd/TEZ 30 mg qd/IVA 45 mg qAM + 50 mg qPM | 0 | -- | 4 | 0.54 | 4 | 0.54 |
| ELX 40 mg qd/TEZ/ 20 mg qd/IVA 30 mg qAM + 25 mg qPM | 0 | -- | 15 | 0.68 | 15 | 0.68 |
| Other ELX combination | 90 | 1.00 | 53 | 4.52 | 143 | 5.52 |
| **Monotherapy (ELX)** | **101** | **2.23** | **0** | -- | **101** | **2.23** |
| ELX <200 mg | 38 | 0.48 | 0 | -- | 38 | 0.48 |
| ELX ≥200 mg | 63 | 1.75 | 0 | -- | 63 | 1.75 |
| **Placebo** | **54** | **2.01** | **378** | **182.55** | **432** | **184.56** |
| **Active Comparators in ELX Studies** | **0** | -- | **271** | **68.78** | **271** | **68.78** |
| TEZ/IVA | 0 | -- | 226 | 61.57 | 226 | 61.57 |
| IVA | 0 | -- | 45 | 7.21 | 45 | 7.21 |

CF: cystic fibrosis; ELX: elexacaftor, also known as VX-445; IVA: ivacaftor, also known as VX-770 or Kalydeco™; PY: person-years; q12h: every 12 hours; qd: once daily; TC: triple combination; TEZ: tezacaftor, also known as VX-661; TEZ/IVA: TEZ in combination with IVA, also known as Symdeko™ or Symkevi ™

Notes: Safety Set includes all subjects who received any amount of elexacaftor alone (monotherapy), elexacaftor in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA) or VX-561 (ELX/TEZ/VX-561), or placebo, or active comparator (TEZ/IVA or IVA) and had the dosing information included in the clinical database by 20 October 2024. A subject may be counted in multiple rows but only once in each row.

[a] Include the following completed healthy volunteer studies with the final CSR TFLs available: 445-001 (Parts A, B, C), 445-002, 445-003, 445-005, 445-006, 445-007, 445-009, 445-011, and 445-012. In groups 2A and 2B in Study VX445-009, moxifloxacin/placebo on Day 1 and Day 16 are regarded as ELX matching placebo. Study 445-007 contains 11 subjects with hepatic impairment.

[b] Include the following completed CF patient studies: 445-001 (Parts D, E, F), 445-102, 445-103, 445-104, 445-105, 445-106, 445-107, 445-109, 445-110, 445-111, 445-113, 445-115, 445-116, 445-117, 445-119, 445-121, 445-124, 445-126 and the following ongoing studies: 445-112, 445-122, 445-125, 121-102, 121-103, and 121-105

**Table 2 Summary of Exposure in the ELX Clinical Development Program by Duration**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| **Duration** | **N = 301** | **Total Exposure (PY)** | **N = 3258** | **Total Exposure (PY)** | **N = 3559** | **Total Exposure (PY)** |
| **Total** | **301** | **6.62** | **3258** | **5895.86** | **3559** | **5902.48** |
| 1 day | 49 | 0.15 | 3 | 0.01 | 52 | 0.15 |
| >1 day to ≤4 weeks | 252 | 6.47 | 591 | 46.76 | 843 | 53.24 |
| >4 weeks to ≤8 weeks | 0 | -- | 63 | 6.67 | 63 | 6.67 |
| >8 to ≤24 weeks | 0 | -- | 95 | 30.07 | 95 | 30.07 |
| >24 to ≤48 weeks | 0 | -- | 133 | 100.96 | 133 | 100.96 |

**Table 2 Summary of Exposure in the ELX Clinical Development Program by Duration**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| **Duration** | **N = 301** | **Total Exposure (PY)** | **N = 3258** | **Total Exposure (PY)** | **N = 3559** | **Total Exposure (PY)** |
| >48 to ≤72 weeks | 0 | -- | 613 | 741.51 | 613 | 741.51 |
| >72 to ≤96 weeks | 0 | -- | 354 | 670.25 | 354 | 670.25 |
| >96 to ≤144 weeks | 0 | -- | 841 | 1939.54 | 841 | 1939.54 |
| >144 to ≤192 weeks | 0 | -- | 140 | 478.42 | 140 | 478.82 |
| >192 weeks | 0 | -- | 425 | 1881.68 | 425 | 1881.68 |
| **Active (combination and monotherapy)** | **247** | **4.61** | **3240** | **5644.53** | **3487** | **5649.14** |
| 1 day | 40 | 0.12 | 3 | 0.01 | 43 | 0.13 |
| >1 day to ≤4 weeks | 207 | 4.49 | 588 | 46.49 | 795 | 50.98 |
| >4 weeks to ≤8 weeks | 0 | -- | 56 | 6.04 | 56 | 6.04 |
| >8 to ≤24 weeks | 0 | -- | 102 | 31.97 | 102 | 31.97 |
| >24 to ≤48 weeks | 0 | -- | 162 | 130.40 | 162 | 130.40 |
| >48 to ≤72 weeks | 0 | -- | 614 | 735.03 | 614 | 735.03 |
| >72 to ≤96 weeks | 0 | -- | 448 | 845.43 | 448 | 845.43 |
| >96 to ≤144 weeks | 0 | -- | 719 | 1631.98 | 719 | 1631.98 |
| >144 to ≤192 weeks | 0 | -- | 224 | 816.17 | 224 | 816.17 |
| >192 weeks | 0 | -- | 324 | 1401.02 | 324 | 1401.02 |
| **Combination (ELX TC)** | **146** | **2.38** | **3240** | **5644.53** | **3386** | **5646.91** |
| 1 day | 3 | 0.01 | 3 | 0.01 | 6 | 0.02 |
| >1 day to ≤4 weeks | 143 | 2.38 | 588 | 46.49 | 731 | 48.86 |
| >4 weeks to ≤8 weeks | 0 | -- | 56 | 6.04 | 56 | 6.04 |
| >8 to ≤24 weeks | 0 | -- | 102 | 31.97 | 102 | 31.97 |
| >24 to ≤48 weeks | 0 | -- | 162 | 130.40 | 162 | 130.40 |
| >48 to ≤72 weeks | 0 | -- | 614 | 735.03 | 614 | 735.03 |
| >72 to ≤96 weeks | 0 | -- | 448 | 845.43 | 448 | 845.43 |
| >96 to ≤144 weeks | 0 | -- | 719 | 1631.98 | 719 | 1631.98 |
| >144 to ≤192 weeks | 0 | -- | 224 | 816.17 | 224 | 816.17 |
| >192 weeks | 0 | -- | 324 | 1401.02 | 324 | 1401.02 |
| **Monotherapy (ELX)** | **101** | **2.23** | **0** | -- | **101** | **2.23** |
| 1 day | 37 | 0.11 | 0 | -- | 37 | 0.11 |
| >1 day to ≤4 weeks | 64 | 2.12 | 0 | -- | 64 | 2.12 |
| >4 weeks to ≤8 weeks | 0 | -- | 0 | -- | 0 | -- |
| >8 to ≤24 weeks | 0 | -- | 0 | -- | 0 | -- |
| >24 to ≤48 weeks | 0 | -- | 0 | -- | 0 | -- |
| >48 to ≤72 weeks | 0 | -- | 0 | -- | 0 | -- |
| >72 to ≤96 weeks | 0 | -- | 0 | -- | 0 | -- |
| >96 to ≤144 weeks | 0 | -- | 0 | -- | 0 | -- |
| >144 to ≤192 weeks | 0 | -- | 0 | -- | 0 | -- |
| >192 weeks | 0 | -- | 0 | -- | 0 | -- |
| **Placebo** | **54** | **2.01** | **378** | **182.55** | **432** | **184.56** |
| 1 day | 9 | 0.03 | 0 | -- | 9 | 0.03 |
| >1 day to ≤4 weeks | 45 | 1.98 | 7 | 0.43 | 52 | 2.40 |
| >4 weeks to ≤8 weeks | 0 | -- | 9 | 0.79 | 9 | 0.79 |
| >8 to ≤24 weeks | 0 | -- | 232 | 114.71 | 232 | 114.71 |
| >24 to ≤48 weeks | 0 | -- | 130 | 66.63 | 130 | 66.63 |
| >48 to ≤72 weeks | 0 | -- | 0 | -- | 0 | -- |
| >72 to ≤96 weeks | 0 | -- | 0 | -- | 0 | -- |
| >96 to ≤144 weeks | 0 | -- | 0 | -- | 0 | -- |

**Table 2 Summary of Exposure in the ELX Clinical Development Program by Duration**

| Duration | Healthy Subjects[a] N = 301 | Healthy Subjects[a] Total Exposure (PY) | Subjects With CF[b] N = 3258 | Subjects With CF[b] Total Exposure (PY) | Overall N = 3559 | Overall Total Exposure (PY) |
|---|---|---|---|---|---|---|
| >144 to ≤192 weeks | 0 | -- | 0 | -- | 0 | -- |
| >192 weeks | 0 | -- | 0 | -- | 0 | -- |
| **Active Comparator in ELX Studies** | **0** | -- | **271** | **68.78** | **271** | **68.78** |
| 1 day | 0 | -- | 0 | -- | 0 | -- |
| >1 day to ≤4 weeks | 0 | -- | 36 | 2.71 | 36 | 2.71 |
| >4 weeks to ≤8 weeks | 0 | -- | 101 | 14.86 | 101 | 14.86 |
| >8 to ≤24 weeks | 0 | -- | 113 | 40.57 | 113 | 40.57 |
| >24 to ≤48 weeks | 0 | -- | 21 | 10.64 | 21 | 10.64 |
| >48 to ≤72 weeks | 0 | -- | 0 | -- | 0 | -- |
| >72 to ≤96 weeks | 0 | -- | 0 | -- | 0 | -- |
| >96 to ≤144 weeks | 0 | -- | 0 | -- | 0 | -- |
| >144 to ≤192 weeks | 0 | -- | 0 | -- | 0 | -- |
| >192 weeks | 0 | -- | 0 | -- | 0 | -- |

CF: cystic fibrosis; ELX: elexacaftor, also known as VX-445; PY: person-years; TC: triple combination

Notes: Safety Set includes all subjects who received any amount of elexacaftor alone (monotherapy), elexacaftor in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA) or VX-561 (ELX/TEZ/VX-561), or placebo, or active comparator (TEZ/IVA or IVA) and had the dosing information included in the clinical database by 20 October 2024. A subject may be counted in multiple rows but only once in each row.

[a] Include the following completed healthy volunteer studies with the final CSR TFLs available: 445-001 (Parts A, B, C), 445-002, 445-003, 445-005, 445-006, 445-007, 445-009, 445-011, and 445-012. In groups 2A and 2B in Study VX445-009, moxifloxacin/placebo on Day 1 and Day 16 are regarded as ELX matching placebo. Study 445-007 contains 11 subjects with hepatic impairment.

[b] Include the following completed CF patient studies: 445-001 (Parts D, E, F), 445-102, 445-103, 445-104, 445-105, 445-106, 445-107, 445-109, 445-110, 445-111, 445-113, 445-115, 445-116, 445-117, 445-119, 445-121, 445-124, 445-126 and the following ongoing studies: 445-112, 445-122, 445-125, 121-102, 121-103, and 121-105

**Table 3 Summary of Exposure in the ELX Clinical Development Program by Age**

| Age (Years) | Healthy Subjects[a] N = 301 | Healthy Subjects[a] Total Exposure (PY) | Subjects With CF[b] N = 3258 | Subjects With CF[b] Total Exposure (PY) | Overall N = 3559 | Overall Total Exposure (PY) |
|---|---|---|---|---|---|---|
| **Total** | **301** | **6.62** | **3258** | **5895.86** | **3559** | **5902.48** |
| ≥1 to <2 years | 0 | -- | 41 | 7.96 | 41 | 7.96 |
| ≥2 to <6 years | 0 | -- | 83 | 212.33 | 83 | 212.33 |
| ≥6 to <12 years | 0 | -- | 241 | 599.73 | 241 | 599.73 |
| ≥12 to <18 years | 0 | -- | 523 | 1092.52 | 523 | 1092.52 |
| ≥18 to <65 years | 300 | 6.59 | 2355 | 3958.64 | 2655 | 3965.23 |
| ≥65 years | 1 | 0.03 | 15 | 24.68 | 16 | 24.71 |
| ≥18 years | 301 | 6.62 | 2370 | 3983.32 | 2671 | 3989.94 |
| **Active (combination and monotherapy)** | **247** | **4.61** | **3240** | **5644.53** | **3487** | **5649.14** |
| ≥1 to <2 years | 0 | -- | 41 | 7.96 | 41 | 7.96 |
| ≥2 to <6 years | 0 | -- | 83 | 212.33 | 83 | 212.33 |
| ≥6 to <12 years | 0 | -- | 241 | 565.17 | 241 | 565.17 |
| ≥12 to <18 years | 0 | -- | 521 | 1041.28 | 521 | 1041.28 |
| ≥18 to <65 years | 246 | 4.58 | 2339 | 3794.09 | 2585 | 3798.67 |
| ≥65 years | 1 | 0.03 | 15 | 23.69 | 16 | 23.72 |
| ≥18 years | 247 | 4.61 | 2354 | 3817.78 | 2601 | 3822.39 |

**Table 3 Summary of Exposure in the ELX Clinical Development Program by Age**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Age (Years) | N = 301 | Total Exposure (PY) | N = 3258 | Total Exposure (PY) | N = 3559 | Total Exposure (PY) |
| **Combination (ELX TC)** | **146** | **2.38** | **3240** | **5644.53** | **3386** | **5646.91** |
| ≥1 to <2 years | 0 | -- | 41 | 7.96 | 41 | 7.96 |
| ≥2 to <6 years | 0 | -- | 83 | 212.33 | 83 | 212.33 |
| ≥6 to <12 years | 0 | -- | 241 | 565.17 | 241 | 565.17 |
| ≥12 to <18 years | 0 | -- | 521 | 1041.28 | 521 | 1041.28 |
| ≥18 to <65 years | 145 | 2.35 | 2339 | 3794.09 | 2484 | 3796.45 |
| ≥65 years | 1 | 0.03 | 15 | 23.69 | 16 | 23.72 |
| ≥18 years | 146 | 2.38 | 2354 | 3817.78 | 2500 | 3820.17 |
| **Monotherapy (ELX)** | **101** | **2.23** | **0** | -- | **101** | **2.23** |
| ≥1 to <2 years | 0 | -- | 0 | -- | 0 | -- |
| ≥2 to <6 years | 0 | -- | 0 | -- | 0 | -- |
| ≥6 to <12 years | 0 | -- | 0 | -- | 0 | -- |
| ≥12 to <18 years | 0 | -- | 0 | -- | 0 | -- |
| ≥18 to <65 years | 101 | 2.23 | 0 | -- | 101 | 2.23 |
| ≥65 years | 0 | -- | 0 | -- | 0 | -- |
| ≥18 years | 101 | 2.23 | 0 | -- | 101 | 2.23 |
| **Placebo** | **54** | **2.01** | **378** | **182.55** | **432** | **184.56** |
| ≥1 to <2 years | 0 | -- | 0 | -- | 0 | -- |
| ≥2 to <6 years | 0 | -- | 0 | -- | 0 | -- |
| ≥6 to <12 years | 0 | -- | 69 | 34.56 | 69 | 34.56 |
| ≥12 to <18 years | 0 | -- | 72 | 35.54 | 72 | 35.54 |
| ≥18 to <65 years | 54 | 2.01 | 236 | 111.96 | 290 | 113.97 |
| ≥65 years | 0 | -- | 1 | 0.49 | 1 | 0.49 |
| ≥18 years | 54 | 2.01 | 237 | 112.45 | 291 | 114.46 |
| **Active Comparator in ELX Studies** | **0** | -- | **271** | **68.78** | **271** | **68.78** |
| ≥1 to <2 years | 0 | -- | 0 | -- | 0 | -- |
| ≥2 to <6 years | 0 | -- | 0 | -- | 0 | -- |
| ≥6 to <12 years | 0 | -- | 0 | -- | 0 | -- |
| ≥12 to <18 years | 0 | -- | 50 | 15.69 | 50 | 15.69 |
| ≥18 to <65 years | 0 | -- | 218 | 52.58 | 218 | 52.58 |
| ≥65 years | 0 | -- | 3 | 0.51 | 3 | 0.51 |
| ≥18 years | 0 | -- | 221 | 53.09 | 221 | 53.09 |

CF: cystic fibrosis; ELX: elexacaftor, also known as VX-445; PY: person-years; TC: triple combination

Notes: Safety Set includes all subjects who received any amount of elexacaftor alone (monotherapy), elexacaftor in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA) or VX-561 (ELX/TEZ/VX-561), or placebo, or active comparator (TEZ/IVA or IVA) and had the dosing information included in the clinical database by 20 October 2024. A subject may be counted in multiple rows but only once in each row.

[a] Include the following completed healthy volunteer studies with the final CSR TFLs available: 445-001 (Parts A, B, C), 445-002, 445-003, 445-005, 445-006, 445-007, 445-009, 445-011, and 445-012. In groups 2A and 2B in Study VX445-009, moxifloxacin/placebo on Day 1 and Day 16 are regarded as ELX matching placebo. Study 445-007 contains 11 subjects with hepatic impairment.

[b] Include the following completed CF patient studies: 445-001 (Parts D, E, F), 445-102, 445-103, 445-104, 445-105, 445-106, 445-107, 445-109, 445-110, 445-111, 445-113, 445-115, 445-116, 445-117, 445-119, 445-121, 445-124, 445-126 and the following ongoing studies: 445-112, 445-122, 445-125, 121-102, 121-103, and 121-105

**Table 4 Summary of Exposure in the ELX Clinical Development Program by Sex**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Sex | N = 301 | Total Exposure (PY) | N = 3258 | Total Exposure (PY) | N = 3559 | Total Exposure (PY) |
| Total | 301 | 6.62 | 3258 | 5895.86 | 3559 | 5902.48 |
| [redacted] | | | | | | |
| Active (combination and monotherapy) | 247 | 4.61 | 3240 | 5644.53 | 3487 | 5649.14 |
| [redacted] | | | | | | |
| Combination (ELX TC) | 146 | 2.38 | 3240 | 5644.53 | 3386 | 5646.91 |
| [redacted] | | | | | | |
| Monotherapy (ELX) | 101 | 2.23 | 0 | -- | 101 | 2.23 |
| [redacted] | | | | | | |
| Placebo | 54 | 2.01 | 378 | 182.55 | 432 | 184.56 |
| [redacted] | | | | | | |
| Active Comparator in ELX Studies | 0 | -- | 271 | 68.78 | 271 | 68.78 |
| [redacted] | | | | | | |

CF: cystic fibrosis; ELX: elexacaftor, also known as VX-445; PY: person-years; TC: triple combination

Notes: Safety Set includes all subjects who received any amount of elexacaftor alone (monotherapy), elexacaftor in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA) or VX-561 (ELX/TEZ/VX-561), or placebo, or active comparator (TEZ/IVA or IVA) and had the dosing information included in the clinical database by 20 October 2024. A subject may be counted in multiple rows but only once in each row.

[a] Include the following completed healthy volunteer studies with the final CSR TFLs available: 445-001 (Parts A, B, C), 445-002, 445-003, 445-005, 445-006, 445-007, 445-009, 445-011, and 445-012. In groups 2A and 2B in Study VX445-009, moxifloxacin/placebo on Day 1 and Day 16 are regarded as ELX matching placebo. Study 445-007 contains 11 subjects with hepatic impairment.

[b] Include the following completed CF patient studies: 445-001 (Parts D, E, F), 445-102, 445-103, 445-104, 445-105, 445-106, 445-107, 445-109, 445-110, 445-111, 445-113, 445-115, 445-116, 445-117, 445-119, 445-121, 445-124, 445-126 and the following ongoing studies: 445-112, 445-122, 445-125, 121-102, 121-103, and 121-105

**Table 5 Summary of Exposure in the ELX Clinical Development Program by Race**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Race | N = 301 | Total Exposure (PY) | N = 3258 | Total Exposure (PY) | N = 3559 | Total Exposure (PY) |
| Total | 301 | 6.62 | 3258 | 5895.86 | 3559 | 5902.48 |
| [redacted] | | | | | | |

**Table 5 Summary of Exposure in the ELX Clinical Development Program by Race**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Race | N = 301 | Total Exposure (PY) | N = 3258 | Total Exposure (PY) | N = 3559 | Total Exposure (PY) |
| Active (combination and monotherapy) | 247 | 4.61 | 3240 | 5644.53 | 3487 | 5649.14 |
| [redacted] | | | | | | |
| Combination (ELX TC) | 146 | 2.38 | 3240 | 5644.53 | 3386 | 5646.91 |
| [redacted] | | | | | | |
| Monotherapy (ELX) | 101 | 2.23 | 0 | -- | 101 | 2.23 |
| [redacted] | | | | | | |

**Table 5 Summary of Exposure in the ELX Clinical Development Program by Race**

| | Healthy Subjects[a] | | Subjects With CF[b] | | Overall | |
|---|---|---|---|---|---|---|
| Race | N = 301 | Total Exposure (PY) | N = 3258 | Total Exposure (PY) | N = 3559 | Total Exposure (PY) |
| Placebo | 54 | 2.01 | 378 | 182.55 | 432 | 184.56 |
| [redacted] | | | | | | |
| Active Comparator in ELX Studies | 0 | -- | 271 | 68.78 | 271 | 68.78 |
| [redacted] | | | | | | |

CF: cystic fibrosis; ELX: elexacaftor, also known as VX-445; PY: person-years; TC: triple combination

Notes: Safety Set includes all subjects who received any amount of elexacaftor alone (monotherapy), elexacaftor in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA) or VX-561 (ELX/TEZ/VX-561), or placebo, or active comparator (TEZ/IVA or IVA) and had the dosing information included in the clinical database by 20 October 2024. A subject may be counted in multiple rows but only once in each row.

[a] Include the following completed healthy volunteer studies with the final CSR TFLs available: 445-001 (Parts A, B, C), 445-002, 445-003, 445-005, 445-006, 445-007, 445-009, 445-011, and 445-012. In groups 2A and 2B in Study VX445-009, moxifloxacin/placebo on Day 1 and Day 16 are regarded as ELX matching placebo. Study 445-007 contains 11 subjects with hepatic impairment.

[b] Include the following completed CF patient studies: 445-001 (Parts D, E, F), 445-102, 445-103, 445-104, 445-105, 445-106, 445-107, 445-109, 445-110, 445-111, 445-113, 445-115, 445-116, 445-117, 445-119, 445-121, 445-124, 445-126 and the following ongoing studies: 445-112, 445-122, 445-125, 121-102, 121-103, and 121-105

# SIV Populations Not Studied in Clinical Trials

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

| Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme | |
|---|---|
| **Acute upper or lower respiratory infections, pulmonary exacerbation, or changes in therapy for sinopulmonary disease within 28 Days before Day 1** | |
| Reason for exclusion | Acute respiratory infections or any adverse pulmonary conditions may alter the results of clinical studies by introducing variability into baseline assessments. |
| Is it to be considered missing information? | No |
| Rationale | ELX/TEZ/IVA did not show unfavourable effects on these conditions during study. ELX/TEZ/IVA improves overall pulmonary condition (ppFEV$_1$ and rate of pulmonary exacerbations, particularly those requiring IV antibiotic treatment and hospitalisation) in patients with CF. |

| Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme | |
|---|---|
| **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 | As a precautionary measure, subjects with abnormal liver function at screening were excluded from clinical studies. |
| Is it to be considered missing information? | Yes |
| Rationale | Hepatoxicity during treatment with ELX/TEZ/IVA is addressed as an important identified risk. Use in subjects with moderate or severe hepatic impairment is considered missing information. |
| **Abnormal renal function** | |
| Reason for exclusion | As a precautionary measure, subjects with abnormal renal function at screening were excluded from clinical studies. |
| Is it to be considered missing information? | No |
| Rationale | Renal excretion is not a major pathway of ELX, TEZ, and IVA elimination, and renal clearance is not expected to play a significant role in the elimination of ELX/TEZ/IVA. |
| **History of prolonged QT 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 experience, ELX/TEZ/IVA did not demonstrate any meaningful change in QTc intervals or any risk of cardiac arrhythmias. |
| **History of solid organ or haematological transplantation** | |
| Reason for exclusion | CF patients who have undergone lung transplantation were excluded from clinical studies as the transplanted lungs have normal CFTR. CF patients with other transplanted organs (e.g., lungs, heart, liver) were also excluded from clinical studies as these patients have significantly different baseline characteristics in terms of disease severity, concomitant therapy, and, in particular, immunosuppression. |
| Is it to be considered missing information? | No |
| Rationale | ELX, TEZ, and IVA have a low potential to cause clinically significant DDIs with the commonly-used immunosuppressants in organ transplantation. In addition, no specific safety concerns are anticipated with the use of ELX/TEZ/IVA in patients with organ transplant. |
| **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 condition, may interfere with study results. |
| Is it to be considered missing information? | No |
| Rationale | ELX/TEZ/IVA improves overall pulmonary condition in CF patients. ELX/TEZ/IVA is not anticipated to have an unfavourable effect on these conditions. |
| **Subjects taking any inhibitors or inducers of CYP3A, including consumption of herbal medications and grapefruit/grapefruit juice, or sensitive substrates of OATP1B1** | |
| Reason for exclusion | ELX, TEZ, and IVA are CYP3A substrates and co-administration with inhibitors or inducers of CYP3A may modify the exposure of ELX/TEZ/IVA and alter study results. ELX is a potential inhibitor of the hepatic transporter OATP1B1 and co-administration with ELX/TEZ/IVA may increase the exposure of substrates of this transporter. |
| Is it to be considered missing information? | No |
| Rationale | The potential interactions between ELX/TEZ/IVA and CYP3A inducers or inhibitors and OATP1B1/B3 substrates have been adequately characterised. |

| Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme |
|---|

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator protein; CYP3A: cytochrome P450 subfamily 3A; ECG: electrocardiogram; ELX: elexacaftor; ELX/TEZ/IVA: ELX in combination with TEZ and IVA; IVA: ivacaftor; LFT: liver function test; OATP1B1/B3: organic anion transporting polypeptides 1B1/1B3; $ppFEV_1$: forced expiratory volume in 1 second; QT: QT interval; QTc: QT interval corrected; TEZ: tezacaftor

## 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 and Breastfeeding women | Pregnant and breastfeeding women were not included in the clinical development programme. |
| Patients with hepatic impairment | A dedicated study (Study 007) evaluating the safety and PK of ELX/TEZ/IVA in 11 subjects without CF who have moderate hepatic impairment has been conducted. Final safety data from this study were generally consistent with the safety data in other subjects treated with ELX/TEZ/IVA.<br>No studies in patients with severe hepatic impairment are planned.<br>In the controlled, Phase 3 studies (Studies 102 and 103) and the open-label extension study (Study 105) in CF subjects 12 years of age and older, 12 subjects with a medical history of portal hypertension, hepatic cirrhosis, and/or portal/hepatic fibrosis received ELX/TEZ/IVA treatment. The safety data in these 12 subjects were generally consistent with the safety data in other subjects treated with ELX/TEZ/IVA.<br>Overall, the safety experience in patients with moderate or severe hepatic impairment is limited. |
| Patients with renal impairment | In the controlled, Phase 3 studies (Studies 102 and 103) and the open-label extension study (Study 105) in CF subjects 12 years of age and older, 2 subjects with a medical history of chronic kidney disease received ELX/TEZ/IVA treatment. Overall, the safety data in these 2 subjects were consistent with the safety data in other subjects treated with ELX/TEZ/IVA. |
| Patients with a disease severity different from inclusion criteria in clinical studies | Clinical studies excluded subjects who had very severe lung dysfunction at Screening (i.e., $ppFEV_1$ <40); however, a small subset of subjects who had $ppFEV_1$ <40 at baseline (predose) were enrolled. In the controlled, Phase 3 studies (Studies 102 and 103) and the open-label extension study (Study 105) in CF subjects 12 years of age and older, 44 subjects with $ppFEV_1$ <40 at baseline received ELX/TEZ/IVA treatment. Overall, the safety data in these 44 subjects were consistent with the safety data in other subjects treated with ELX/TEZ/IVA. |
| Population with relevant different ethnic origin | CF is a disease occurring primarily in Caucasians, and the population studied in the clinical studies was racially and ethnically representative of the CF population in general. |

$AUC_\tau$: area under the concentration versus time curve; CF: cystic fibrosis; $C_{max}$: maximum observed concentration; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; Study 007: VX18-445-007; Study 102: VX17-445-102; Study 103: VX17-445-103; Study 105: VX17-445-105

# SV Post-authorisation Experience

## SV.1 Post-authorisation Exposure

### *SV.1.1 Method Used to Calculate Exposure*

Cumulative post-authorisation exposures were estimated using data at the time of distribution, not necessarily the time of usage. There might be a delay between the time a medication was distributed and the time a medication was used by a patient. Caution must be exercised when using post-authorisation exposure estimates to evaluate spontaneous reports. The methodology used for estimating post-authorisation exposure may vary by geographic region, as described below.

**Methods used to calculate exposure – European Economic Area, UK, Australia, Brazil, Switzerland, Israel, and Rest of World**

The exposure estimate includes patients who initiated Trikafta/Kaftrio treatment via commercial supply only. The person-days estimate is based on initial delivery and re-order supply data using the following approach:

The number of days of treatment supplied for patients initiated during the commercial supply period (varies from country to country) enumerated over all patients. Compliance is calculated based on the number of patients exposed to ELX/TEZ/IVA, comparing the expected number of packs sold to the actual number of packs sold. This compliance calculation is used when estimating the total person-days. The cumulative exposure is calculated using the estimated patients initiated onto therapy, while the period exposure is calculated using the patients who remain on therapy. Cumulative exposure was estimated between the date of MA approval in each region/country and 20 October 2024. Of note, the distribution by age and sex were not available due to privacy restrictions.

**Methods used to calculate exposure – US and Canada**

The exposure estimate includes patients who initiated Trikafta treatment via commercial supply only. The person-days estimate is based on initial delivery, and re-orders supply data. US cumulative exposure was estimated from 21 October 2019 to 20 October 2024. Due to the Health Insurance Portability and Accountability Act regulations and provider reporting practices in the US, genotype data are not available.

Canadian cumulative exposure data was estimated from 18 June 2021 through 20 October 2024.

**Global Compassionate Use**

The exposure estimate includes patients who initiated ELX/TEZ/IVA treatment via compassionate programs (e.g., expanded access programs, managed access programs [MAP], named patient programs, and Early Access Program [AP; France]). The PYs estimate is based on initial delivery and refill supply data. The cumulative exposure was estimated through 20 October 2024.

### *SV.1.2 Exposure*

Worldwide cumulative patient exposure to ELX/TEZ/IVA from marketing experience is presented in Table 6. Overall, approximately 79,082 patients were exposed to ELX/TEZ/IVA worldwide since the first authorisation of ELX/TEZ/IVA: [redacted] patients in the US, 24,486 patients in the EEA, [redacted] patients in the UK, [redacted] patients in Canada, [redacted] patients in Australia, [redacted] patients in Switzerland, [redacted] patients in Israel, [redacted] patients in Brazil, and

3,588 patients in the rest of the world (via early access programs). Additionally, there were 3,185 patients who received ELX/TEZ/IVA via compassionate use programs globally.

Cumulative patient exposures are provided for the EEA, and UK by country in Table 7. Cumulative patient exposures for the US and Canada by age and sex are provided in Table 8 and Table 9.

Overall, the post-authorisation safety data are generally consistent with the established safety profile of ELX/TEZ/IVA.

**Table 6 Estimated Worldwide Cumulative Patient Exposure to ELX/TEZ/IVA From Marketing Experience**

| Region/Country | Patients | Person-Years (Estimated) |
|---|---|---|
| US | [redacted] | |
| EEA[a] | 24,486 | 53,962 |
| UK | [redacted] | |
| Canada | | |
| Australia | | |
| Switzerland | | |
| Israel | | |
| Brazil | | |
| Chile | | |
| Russia | | |
| Uruguay | | |
| New Zealand | | |
| Rest of World[b] | 1,006 | 1,012 |
| Compassionate Use | 3,185 | 3,165 |
| **Total** | **79,082** | **190,738** |

EEA: European Economic Area; ELX/TEZ/IVA: Elexacaftor in combination with tezacaftor and ivacaftor; UK: United Kingdom; US: United States.

[a] Includes Norway, Iceland, and Liechtenstein through EEA agreement (Decision N° 74/1999 of the EEA Joint Committee)

[b] Rest of World includes Argentina, Bosnia and Herzegovina, Colombia, Macedonia, Montenegro, Saudi Arabia, South Africa, Turkey, and United Arab Emirates.

**Table 7 Estimated Cumulative Patient Exposure to ELX/TEZ/IVA from Marketing Experience in the EEA and UK by Country**

| Country | Patients | Person-years (Estimated) |
|---|---|---|
| Austria | [redacted] | |
| Belgium | | |
| Bulgaria | | |
| Croatia | | |
| Cyprus | | |
| Czech Republic | | |
| Denmark | | |
| Estonia | | |
| Finland | | |
| France | | |
| Germany | | |
| Greece | | |
| Hungary | | |
| Iceland | | |
| Italy | | |
| Latvia | | |

**Table 7 Estimated Cumulative Patient Exposure to ELX/TEZ/IVA from Marketing Experience in the EEA and UK by Country**

| Country | Patients | Person-years (Estimated) |
|---|---|---|
| Lithuania | [redacted] | |
| Luxembourg | | |
| Malta | | |
| Norway | | |
| Poland | | |
| Portugal | | |
| Romania | | |
| Republic of Ireland | | |
| Serbia | | |
| Slovakia | | |
| Slovenia | | |
| Spain | | |
| Sweden | | |
| The Netherlands | | |
| **UK** | | |
| England | | |
| Scotland | | |
| Wales | | |
| Northern Ireland | | |
| UK Crown Dependencies | | |
| Gibraltar | | |
| **Total** | **33,766** | **79,676** |

EEA: European Economic Area; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; UK: United Kingdom

**Table 8 Estimated Cumulative Patient Exposure to ELX/TEZ/IVA from Marketing Experience in the US by Age and Sex**

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

ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; PY: person-years; US: United States

[a] The total column includes patients for whom sex and/or age are unknown.

**Table 9 Estimated Cumulative Patient Exposure to ELX/TEZ/IVA from Marketing Experience in Canada, by Age and Sex**

| | [redacted] | | [redacted] | | [redacted] | | **Total[a]** | |
|---|---|---|---|---|---|---|---|---|
| **Age** | **Patients** | **PY** | **Patients** | **PY** | **Patients** | **PY** | **Patients** | **PY** |
| <2 years | [redacted] | | | | | | | |
| ≥2 to <6 years | | | | | | | | |
| ≥6 to <12 years | | | | | | | | |
| ≥12 to <18 years | | | | | | | | |
| ≥18 years | | | | | | | | |

**Table 9 Estimated Cumulative Patient Exposure to ELX/TEZ/IVA from Marketing Experience in Canada, by Age and Sex**

| | [redacted] | | [redacted] | | [redacted] | | Total[a] | |
|---|---|---|---|---|---|---|---|---|
| **Age** | **Patients** | **PY** | **Patients** | **PY** | **Patients** | **PY** | **Patients** | **PY** |
| Unknown | [redacted] | | | | | | | |
| **Total** | | | | | | | | |

ELX/TEZ/IVA: Elexacaftor in combination with tezacaftor and ivacaftor; PY: person-years; US: United States.
[a] The total column includes patients for whom sex and/or age are unknown.

### *SV.1.3 IVA Monotherapy Post-authorisation Exposure*

Worldwide cumulative marketing exposure for IVA monotherapy as of 23 January 2025 includes 10,680 patients, representing 35,178.7 person-years.

# SVI Additional EU Requirements for Safety Specification

**Potential for Misuse for Illegal Purposes**

No systematic examination of the abuse potential of ELX, TEZ, or IVA was performed in the ELX nonclinical and clinical development programmes. Nonclinical studies did not demonstrate any evidence of neurobehavioural side effects. Evaluation of adverse events (AEs) in clinical studies did not reveal any evidence of euphoria, sedation, or mood alteration.

Therefore, ELX/TEZ/IVA use is not expected to have the potential for misuse for illegal purposes.

ELX/TEZ/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 following risks are described in Section 4.8 (Undesirable Effects) of the EU Summary of Product Characteristics (SmPC), but are not considered to be important risks given the events in clinical studies were mostly mild to moderate in severity and non-serious, with few study drug discontinuations; therefore, they are not expected to have a significant impact on the ELX/TEZ/IVA benefit-risk profile:

- Upper respiratory tract infection
- Headache
- Nasal congestion
- Rhinorrhoea
- Diarrhoea
- Abdominal pain
- Rash
- Blood creatine phosphokinase increased
- Rhinitis
- Abdominal pain upper
- Flatulence
- Hypoglycaemia

- Acne
- Dizziness
- Pruritus
- Wheezing
- Respiration abnormal (abnormal breathing)

In the 24-week, placebo-controlled, Phase 3 study in CF subjects 12 years of age and older (VX17-445-102 [Study 102]), a modest increase from baseline in mean BP was observed in the ELX/TEZ/IVA group (systolic BP increased between 2.0 mm Hg and 3.5 mm Hg). The incidence of subjects in the hypertensive range was similar between the ELX/TEZ/IVA and placebo groups, with few AEs of BP increased reported overall. As such, the modest increase in mean BP observed in this normotensive population is unlikely to be clinically relevant or have a significant impact on the benefit risk profile (Module 2.5).

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

Descriptions of the initially proposed important identified and important potential risks and missing information for ELX/TEZ/IVA are provided herein; changes to the initially approved RMP will be captured in Section SVII.2.

#### *SVII.1.2.1 Important Identified Risk – Susceptibility for influenza virus infections*

**Benefit-Risk Impact**
In the 24-week, placebo-controlled Phase 3 study in CF subjects 12 years of age and older (Study 102), a higher incidence of influenza AEs was reported in the ELX/TEZ/IVA group compared to the placebo group. In the ELX/TEZ/IVA group, all AEs of influenza were mild or moderate in severity and most were non-serious. All subjects continued ELX/TEZ/IVA dosing or resumed treatment after an interruption. In the open-label extension Study 105, the rate of influenza AEs during extended ELX/TEZ/IVA treatment was lower than the rate in the ELX/TEZ/IVA group in Study 102, and similar to the rate in the placebo group in Study 102.

Based on the overall safety experience with ELX/TEZ/IVA, an association between treatment and influenza cannot be completely excluded. As such, susceptibility for influenza virus infections is considered an important identified risk.

#### *SVII.1.2.2 Important Potential Risk – Hepatotoxicity*

**Benefit-Risk Impact**
In the 24-week, placebo-controlled Phase 3 study in CF subjects 12 years of age and older (Study 102), a higher incidence of elevated transaminase AEs was reported in the ELX/TEZ/IVA group compared to the placebo group. In addition, the incidence of ALT and/or aspartate aminotransferase (AST) laboratory elevations >3 × upper limit of normal (ULN) was higher in the ELX/TEZ/IVA group than in the placebo group. LFT elevations were also seen in other clinical studies with ELX/TEZ/IVA, including the open-label extension Study 105.

The overall safety experience with ELX/TEZ/IVA does not suggest a causal association between treatment and hepatotoxicity; however, the potential for hepatotoxicity cannot be excluded. As such, hepatotoxicity is considered an important potential risk.

### *SVII.1.2.3 Important Potential Risk – Cataract*

**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 in paediatric subjects treated with IVA-containing regimens during clinical studies and post-authorisation 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, the high prevalence of background lens opacities, the subtlety of the ophthalmological findings, and/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 finding. Therefore, cataracts are considered an important potential risk.

### *SVII.1.2.4 Missing Information – Use in Pregnant and Lactating Women*

**Benefit-Risk Impact**
Nonclinical studies indicated that ELX, TEZ, and IVA are not teratogens. Additional nonclinical studies showed ELX, TEZ, and IVA were transferred to the placenta of pregnant rats and execrated into the milk of lactating rats.

The effect of ELX/TEZ/IVA on pregnancy and lactation in humans is not known as no clinical studies in pregnant or lactating women have been conducted. Therefore, the safety in this population is considered missing information and further characterisation is needed.

### *SVII.1.2.5 Missing Information – Long-term Safety*

**Benefit-Risk Impact**
The longest clinical study experience with ELX/TEZ/IVA treatment is approximately 69 weeks.

As a chronic treatment, the long-term safety of ELX/TEZ/IVA is considered missing information and further characterisation is needed.

### *SVII.1.2.6 Missing Information – Use in Patients With Moderate or Severe Hepatic Impairment*

**Benefit-Risk Impact**
A dedicated study (VX18-445-007 [Study 007]) has been conducted to evaluate the safety and PK of ELX/TEZ/IVA in 11 subjects without CF who have moderate hepatic impairment. Based on the preliminary results from this study, the mean $AUC_{\tau}$ for total ELX increased 1.25-fold, while $C_{max}$ was similar in subjects with moderate hepatic impairment relative to matched healthy subjects. Mean exposures ($AUC_{\tau}$ and $C_{max}$) of total M23-ELX increased approximately 1.7-fold in subjects with moderate hepatic impairment relative to matched healthy subjects. Mean $AUC_{\tau}$ for total ELX+M23-ELX increased 1.36-fold, while $C_{max}$ increased 1.24-fold in subjects with moderate hepatic impairment relative to matched healthy subjects.

In the controlled, Phase 3 studies (Studies 102 and 103) and the open-label extension study (Study 105) in CF subjects 12 years of age and older, 12 subjects with a medical history of portal hypertension, hepatic cirrhosis, and/or portal/hepatic fibrosis received ELX/TEZ/IVA

treatment. The safety data in these 12 subjects were generally consistent with the safety data in other subjects treated with ELX/TEZ/IVA.

Overall, the safety experience in patients with moderate or severe hepatic impairment is limited; therefore, the use of ELX/TEZ/IVA in this population 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 – Hepatotoxicity*

Post-marketing reports of drug-induced liver injury have been received in patients treated with ELX/TEZ/IVA, including cases of liver injury characterized by concurrent elevations of transaminases and bilirubin, and one case of [redacted]. An association with ELX/TEZ/IVA treatment cannot be excluded in these cases. As such, the important potential risk of "Hepatoxicity" is being reclassified to an important identified risk in the EU RMP Version 3.1.

### *SVII.2.2 Added Missing Information – Use in children aged 6 to 11 years*

A line extension submission and a Type II variation for ELX/TEZ/IVA use in children aged 6 to 11 years was submitted on 8 March 2021 (EMEA/H/C/5269/X/0008/G). During the assessment, PRAC requested that the summary of safety concerns be updated to include "Use in children aged 6 to 11 years" as missing information for ELX/TEZ/IVA. As such, the summary of safety concerns was updated to include it in EU RMP v4.0.

### *SVII.2.2 Updated Missing Information – 'Use in children aged 6 to 11 years' to 'Use in children aged 2 to 11 years'*

The missing information of 'Use in children aged 6 to 11 years' was updated to 'Use in children aged 2 to 11 years' during the line extension submission for ELX/TEZ/IVA use in children aged 2 to 5 years. As such, the summary of safety concerns was also updated to include it in EU RMP v6.2.

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

### *SVII.3.1 Presentation of Important Identified Risks*

#### *SVII.3.1.1 Important Identified Risk – Susceptibility for Influenza Virus Infections*

**Potential mechanisms**
No potential mechanism has been identified.

Influenza is one of the most common infectious illnesses worldwide. The Centers for Disease Control and Prevention estimates that the burden of influenza illness during the 2018 to 2019 season included an estimated 35.5 million people getting sick with influenza, 16.5 million people going to a health care provider for their illness, 490,600 hospitalisations, and 34,200 deaths from influenza.[63]

**Evidence source(s) and strength of evidence**
In the 24-week, placebo-controlled Phase 3 study in CF subjects 12 years of age and older (Study 102), a higher incidence of influenza AEs was reported in the ELX/TEZ/IVA group compared to the placebo group. In the ELX/TEZ/IVA group, all AEs of influenza were mild or moderate in severity and most were non-serious. All subjects continued ELX/TEZ/IVA

dosing or resumed treatment after an interruption. In the open-label extension Study 105, the rate of influenza AEs during extended ELX/TEZ/IVA treatment was lower than the rate in the ELX/TEZ/IVA group in Study 102, and similar to the rate in the placebo group in Study 102.

**Characterisation of the risk**

**Phase 3, Controlled Studies in CF Subjects 12 Years of Age and Older**

In the 24-week, placebo-controlled study in CF subjects who are heterozygous for the *F508del* mutation in the *CFTR* gene with a minimal function mutation (F/MF genotype) (Study 102), a higher incidence of influenza AEs was reported in the ELX/TEZ/IVA group (6.9%) compared to the placebo group (1.5%). In the ELX/TEZ/IVA group, all AEs of influenza were mild or moderate in severity and most were non-serious; 3 (1.5%) subjects had AEs of influenza that were serious. All subjects with AEs of influenza continued ELX/TEZ/IVA dosing or resumed treatment after an interruption.

In the 4-week, TEZ/IVA-controlled study in CF subjects who are homozygous for the *F508del* mutation in the *CFTR* gene (F/F genotype) (VX17-445-103 [Study 103]), there were no AEs of influenza in the ELX/TEZ/IVA group.

In the 8week, IVA and TEZ/IVA-controlled study in CF subjects who are heterozygous for the *F508del* mutation in the *CFTR* gene with a gating or residual function mutation (F/Gating or F/RF genotypes, respectively) (VX18445104 [Study 104]), the incidence of influenza AEs was balanced between the ELX/TEZ/IVA group (2 subjects [1.5%]) and the control group (2 subjects [1.6%]). In the ELX/TEZ/IVA group, both AEs of influenza were mild in severity and nonserious; neither event led to a change in ELX/TEZ/IVA dosing.

**Phase 3, Open-label Extension Study in CF Subjects 12 Years of Age and Older**

In the open-label extension Study 105 in CF subjects who previously completed Study 102 (*F*/MF genotype) or Study 103 (*F/F* genotype), final results from the 192-week analysis showed the exposure-adjusted event rate for influenza (4.38 events/100PY) was substantially lower than the rate in the ELX/TEZ/IVA group of Study 102 (15.97 events/100PY). Additionally, the rate of influenza in Study 105 was similar to the rate in the placebo group of Study 102 (3.00 events/100PY).

In Study 105, the majority of influenza AEs were mild or moderate in severity and nonserious; 7 (1.4%) subjects had AEs of influenza that were serious. None of the influenza AEs led to interruption or discontinuation of ELX/TEZ/IVA treatment.

Overall, there was a lower rate of influenza AEs in the open-label extension Study 105 compared to the parent Study 102; the nature and severity of these AEs remained consistent with extended ELX/TEZ/IVA treatment.

**Phase 3 Study in subjects aged 6 to 11 years**

In the 24-week, open-label, Phase 3 Study 106 Part B in subjects aged 6 through 11 years of age, 7 (10.6%) subjects had AEs of influenza. All influenza AEs were mild or moderate in severity, and none were serious or led to treatment interruption or discontinuation.

Overall, results relevant to influenza from Study 106 Part B were generally consistent with the results from the prior studies in subjects ≥12 years of age (Studies 102 and 103).

**Phase 3, Open-label Extension Study in CF Subjects 6 Years of Age and Older**

In the open-label extension Study 107 in CF subjects who previously completed Study 106, final results from the 192-week analysis showed the exposure adjusted event rate for

influenza (3.34 events/100PY) was substantially lower than the rate in the ELX/TEZ/IVA group of Study 106 (23.16 events/100PY).

In Study 107, there were 7 AEs of influenza which were all mild in severity and non-serious, and did not lead to interruption or discontinuation of ELX/TEZ/IVA treatment.

Overall, there was a lower rate of influenza AEs in the open-label extension Study 107 compared to the parent Study 106; the nature and severity of these AEs remained consistent with extended ELX/TEZ/IVA treatment.

**Phase 3 Study in subjects aged 2 to 5 years**

In the 24-week, open-label, Phase 3 Study 111 Part B in subjects aged 2 through 5 years of age, 1 (1.3%) subject had a nonserious AE of influenza, which was moderate in severity, and resolved without treatment interruption or discontinuation. Overall, results relevant to influenza from Study 111 Part B were generally consistent with results from prior studies in older subjects.

**Phase 3, Open-label Extension Study in CF Subjects 2 Years of Age and Older**

In the open-label extension Study 112 in CF subjects who previously completed Study 111 Part B, final results from the 96-week analysis showed the exposure adjusted event rate for influenza (9.85 events/100PY) was within the range of exposure-adjusted rates of influenza in other VX-445 studies and in the general population.[64]

In Study 112, there were 11 AEs of influenza; most were mild or moderate in severity and non-serious, and did not lead to interruption or discontinuation of ELX/TEZ/IVA treatment. There was one event of [redacted] that was considered both serious and severe which occurred concurrently with a [redacted] and [redacted] The events required [redacted] and treatment and resolved without change to ELX/TEZ/IVA treatment.

Overall, the rate of influenza AEs in the open-label extension Study 112 was consistent with the data observed in previous studies of ELX/TEZ/IVA; the nature and severity of these AEs remained generally consistent with extended ELX/TEZ/IVA treatment.

**Phase 3 Study in CF subjects with non-*F508del* mutation in the *CFTR* gene**

In the 24-week, placebo-controlled Phase 3 Study 124 in subjects aged 6 years and older with a non-*F508del* ELX/TEZ/IVA-responsive *CFTR* mutation, 18 (8.8%) subjects in the ELX/TEZ/IVA treatment arm had an AE of influenza compared to 2 (2.0%) subjects in the placebo group. The results in Study 124 were generally consistent with the previous study experience in pivotal Study 102.

**Risk factors and risk groups**

Patients who are hospitalised frequently or for long-term durations are at a greater risk for contracting influenza from other infected individuals. Risk factors for influenza-related complications include common CF comorbidities (e.g., chronic lung disease, asthma) and a compromised immune system.

**Preventability**

The most effective way to prevent influenza is to get an annual vaccination.

**Impact on the benefit-risk balance of the product**

Given the broad (pulmonary and systemic) clinical benefits demonstrated with ELX/TEZ/IVA treatment, and the generally mild to moderate nature of the influenza AEs observed in clinical studies, this risk is not expected to significantly impact the benefit-risk balance.

Influenza is listed as an adverse drug reaction in Section 4.8 of the SmPC. 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 anticipated.

### *SVII.3.1.2 Important Identified Risk – Hepatotoxicity*

**Potential mechanisms**
ELX, TEZ, and IVA are primarily metabolised by liver enzymes; however, the exact mechanism of the effect of ELX/TEZ/IVA on LFTs is not presently known.

Common comorbidities in patients with CF and use of certain concomitant medications may contribute to the increase in LFTs.

**Evidence source(s) and strength of evidence**
In the 24-week, placebo-controlled, Phase 3 study in CF subjects 12 years of age and older (Study 102), the incidence of elevated transaminase events (AEs or ALT/AST laboratory elevations >3 × ULN) was higher in the group of subjects treated with ELX/TEZ/IVA than in the group of subjects receiving placebo. LFT elevations were also seen in other clinical studies with ELX/TEZ/IVA, including the open-label extension Study 105.

In addition, post-marketing reports of drug-induced liver injury have been received in patients treated with ELX/TEZ/IVA, including cases of liver injury characterized by concurrent elevations of transaminases and bilirubin, and cases of liver failure leading to transplantation in a patients with and without pre-existing advanced liver disease. An association with ELX/TEZ/IVA treatment cannot be excluded in these cases.

**Characterisation of the risk**
**Phase 3, Controlled Studies in CF Subjects 12 Years of Age and Older**
In the 24-week, placebo-controlled study in CF patients 12 years of age and older who have an F/MF genotype (Study 102), elevated transaminase AEs occurred at a higher incidence in the ELX/TEZ/IVA group than in the placebo group (10.9% versus 4.0%, respectively). The majority of these events were mild or moderate in severity and associated with ALT/AST elevations <5 × ULN.

There were no elevated transaminase events that led to treatment discontinuation.
Two (1.0%) subjects in the ELX/TEZ/IVA group and 3 (1.5%) subjects in the placebo group had elevated transaminase events that led to treatment interruption: 1 of the subjects in the ELX/TEZ/IVA group resumed treatment; the other subject enrolled in the openlabel extension study (Study 105) while still on study drug interruption and eventually discontinued from that study without resuming study drug.

No subjects in the ELX/TEZ/IVA group and 1 subject (0.5%) in the placebo group had a serious elevated transaminase event.

The incidence of ALT/AST laboratory elevations >3 × ULN was higher in the ELX/TEZ/IVA group than in the placebo group (7.9% versus 5.5%, respectively), while the incidences of ALT/AST >5 × ULN and >8 × ULN were generally comparable between treatment groups (2.5% and 1.5% in the ELX/TEZ/IVA group, respectively, versus 1.5% and 1.0% in the placebo group).

No subject had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN.

Results relevant to LFT assessment from studies in CF subjects who have *F/F* genotype (Study 103) or who have an F/Gating or F/RF genotype (Study 104) were generally consistent with those from Study 102.

**Phase 3, Open-label Extension Study in CF Subjects 12 Years of Age and Older**

In the open-label extension Study 105 in CF subjects who previously completed Study 102 (*F*/MF genotype) or Study 103 (*F/F* genotype), final results from the 192-week analysis showed the exposure-adjusted event rate for elevated transaminase AEs was lower in Study 105 than in the Study 102 ELX/TEZ/IVA group (10.07 and 42.92 events/100PY, respectively). Additionally, the severity and magnitude of the ALT/AST elevations associated with these AEs in Study 105 were similar to those in the parent studies.

Elevated transaminase events led to treatment interruption in 21 (4.2%) subjects and led to treatment discontinuation in 7 (1.4%) subjects.

The incidence of subjects with maximum on-treatment transaminase elevations (ALT and/or AST) above thresholds of >3 ×, >5 ×, and >8 × ULN were 12.5%, 7.1% and 2.2%, respectively.

Two (0.6%) subjects had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN.

Overall, results relevant to LFT assessment from open-label extension Study 105 were generally consistent with the results from the parent studies (Studies 102 and 103).

**Phase 3 Study in subjects aged 6 to 11 years**

In the 24-week, open-label, Phase 3 Study 106 Part B in subjects aged 6 through 11 years of age, 7 (10.6%) subjects had elevated transaminase events. All of the events were mild or moderate in severity, and none were serious or led to treatment discontinuation or interruption. Seven (10.6%) subjects had ALT or AST >3 × ULN, and 1 (1.5%) subject had ALT or AST >5 × ULN; no subjects had ALT or AST >8 × ULN. The majority of subjects had bilirubin values that remained within the normal range; no subjects had total bilirubin >2 × ULN.

Overall, results relevant to LFT assessment from Study 106 Part B were generally consistent with the results from the prior studies in subjects ≥12 years of age (Studies 102 and 103).

**Phase 3, Open-label Extension Study in CF Subjects 6 Years of Age and Older**

Final results from 192 weeks of treatment in open-label extension Study 107 evaluating subjects aged 6 years and older were generally consistent with those seen in parent Study 106 and the pivotal Study 102 in subjects 12 years and older. AEs of elevated transaminases occurred in 6 (9.4%) subjects, all of which were mild to moderate in severity and there were no serious events. One AE of ALT increased led to discontinuation of study drug and no events led to treatment interruption. Exposure-adjusted elevated transaminase events in Study 107 (7.64 events/100 PY) were lower than in the parent study (31.84 events/100 PY).

Elevation of ALT or AST >3, >5, and >8 × ULN occurred in 6 (9.4%), 3 (4.7%), and 1 (1.6%) subject(s), respectively. No subjects had elevation of ALT or AST >3 × ULN concurrent with newly occurred elevation of total bilirubin >2 × ULN.

Overall, results relevant to LFT assessment from openlabel extension Study 107 were generally consistent with the results from the Parent Study 106.

**Phase 3 Study in subjects aged 2 to 5 years**

In the 24-week, open-label, Phase 3 Study 111 Part B in subjects aged 2 through 5 years of age, 8 (10.7%) subjects had elevated transaminase events. All elevated transaminase events were mild or moderate in severity, and none were serious or led to treatment discontinuation. One subject interrupted study drug due to AEs of [redacted], which were all mild in severity and assessed by the investigator as not related. Six (8.0%) subjects had ALT or AST >3 × ULN, 2 (2.7%) subjects had ALT or AST >5× ULN, and 1 (1.3%) subject had ALT or AST >8 × ULN. No subject had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN.

Overall, results relevant to LFT assessment from Study 111 Part B were generally consistent with the results from prior studies.

**Phase 3, Open-label Extension Study in CF Subjects 2 Years of Age and Older**

Final results from 96 weeks of treatment in open-label extension Study 112 evaluating subjects aged 2 years and older were generally consistent with those seen in parent Study 111 Part B and the pivotal Study 102 in subjects 12 years and older. AEs of elevated transaminases occurred in 8 (11.4%) subjects, all of which were mild to moderate in severity and there were no serious events. One subject had AEs of [redacted] which led to discontinuation of study drug and no events led to treatment interruption. Exposure-adjusted rate of elevated transaminase events in Study 112 (8.33 events/100 PY) were lower than in the parent study (42.04 events/100 PY).

Elevation of ALT or AST >3, >5, and >8 × ULN occurred in 7 (10.0%), 1 (1.4%), and 0 subject(s), respectively. No subjects had elevation of ALT or AST >3 × ULN concurrent with newly occurred elevation of total bilirubin >2 × ULN.

Overall, results relevant to LFT assessment from open-label extension Study 112 were generally consistent with the results from the Parent Study 111 Part B.

**Phase 3 Study in CF subjects with non-*F508del* mutation in the *CFTR* gene**

In the 24-week, placebo-controlled Phase 3 Study 124 in subjects aged 6 years and older with a non-*F508del* ELX/TEZ/IVA-responsive *CFTR* mutation, AEs of elevated transaminases occurred in 8 (3.9%) subjects in the ELX/TEZ/IVA group and no subjects in the placebo group. In the ELX/TEZ/IVA group, 1 (0.5%) subject had elevated transaminase events that led to treatment discontinuation. Three (1.5%) subjects had elevated transaminase events that led to treatment interruption.

All AEs were mild to moderate in severity, and none were serious. Elevation of ALT or AST >3, >5, and >8 × ULN occurred in 13 (6.3%), 4 (2.0%), and 4 (2.0%) subjects, respectively. No subjects had elevation of ALT or AST >3 × ULN concurrent with newly occurred elevation of total bilirubin >2 × ULN.

Overall, results relevant to LFT assessment from Study 124 were generally consistent with the results from prior studies.

**Post-marketing Experience**

Post-marketing reports of drug-induced liver injury have been received in patients treated with ELX/TEZ/IVA, including cases of liver injury characterized by concurrent elevations of transaminases and bilirubin, and cases of liver failure leading to transplantation in patients with and without pre-existing advanced liver disease. An association with ELX/TEZ/IVA treatment cannot be excluded in these cases.

**Risk factors and risk groups**

Generally known risk factors for increases in transaminases include concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, viral hepatitis), comorbidities (e.g., CF liver disease), and use of concomitant drugs (e.g., acetaminophen, antibiotics) or substances (alcohol) known to be associated with liver enzyme elevations. Patients with pre-existing advanced liver disease (e.g., cirrhosis and portal hypertension) may be at an increased risk of developing severe liver injury such as liver failure requiring transplantation.

**Preventability**

Appropriate monitoring of LFTs and drug interruptions or discontinuations are the standard measures to detect and prevent drug-induced liver injury.

**Impact on the benefit-risk balance of the product**

Elevated transaminases with ELX/TEZ/IVA treatment were generally transient and resolved without long-term sequelae. Very high levels of transaminase elevations or transaminase elevations with concurrent total bilirubin elevation may be a sign of liver injury which could become permanent or be life-threatening. There is also the risk of more severe liver injury including liver injury leading to transplant in patients with underlying advanced liver disease.

Given the broad (pulmonary and systemic) clinical benefits demonstrated with ELX/TEZ/IVA treatment, the the rarity of cases of liver injury, and the monitorability of LFTs in clinical practice, and the guidance regarding risks in patients with underlying advanced liver disease, this risk is not expected to significantly impact the benefit-risk balance.

The identified risk of hepatotoxicity is described in the product information, along with recommendations for LFT monitoring in all patients and more frequent monitoring in patients with a history of elevated transaminases or underlying liver disease. 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 anticipated.

### *SVII.3.2 Presentation of Important Potential Risks*

#### *SVII.3.2.1 Important Potential Risk – Cataract*

**Potential mechanisms**

The aetiology for the observation of IVA-induced cataracts in juvenile rats (without evidence of cataracts after chronic dosing in adult rats) is unknown; however, it is likely related to factors specific to the development of lens tissues in the eye of albino rats. One hypothesis to explain this observation 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**

Cataracts (lens opacities) considered related to IVA treatment were seen during studies in newborn rats but were not observed in older animals or in longer duration animal studies.

Given developmental differences between rats and humans, it is unlikely that the cataract finding is relevant to humans 2 years of age and older.

Non-congenital cataracts without impact on vision have been reported in paediatric subjects treated with IVA-containing regimens during clinical studies and post-authorisation surveillance, but the relationship of these events to treatment is uncertain due to the presence of other possible causes.

**Characterisation of the risk**
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.

In humans, a small number of non-congenital cataract events were reported in paediatric subjects treated with IVA-containing regimens from clinical studies and -post-authorisation surveillance. However, the relationship of these events to IVA is uncertain due to lack of baseline ophthalmological examinations, the high prevalence of background lens opacities, the subtlety of the ophthalmological findings, and the presence of other confounding risk factors (e.g., corticosteroid use, history of uncontrolled diabetes). In addition, results from an ocular safety study with IVA monotherapy showed a lack of cataract progression in patients treated with IVA monotherapy based on the Lens Opacity Classification System, Version III grading.

Ophthalmologic examinations are routinely conducted in the ELX/TEZ/IVA trials in subjects aged <18 years on the date of informed consent signing. In the long-term extension Study 105 in subjects aged 12 years and older, final results from the 192-week analysis showed 3 (0.6%) subjects had an AE of cataract, and 2 (0.4%) subjects had an AE of cataract cortical. All events were mild or moderate in severity, nonserious, and assessed by the investigator as related or possibly related to study drug. None of the events required treatment or led to study drug interruption or discontinuation. Final results from 192 weeks of treatment in open-label extension Study 107 evaluating subjects aged 6 years and older showed 6 (9.4%) subjects had events related to lenticular opacity or cataracts; lenticular opacities in 3 subjects, cataract in 2 subjects, cataract cortical in 1 subject, and cataract nuclear in 1 subject. None of these events were reported as clinically significant. One AE of lenticular opacities was assessed by the investigator as not related to study drug; all remaining AEs were assessed as possibly related. All AEs were mild and did not require treatment or lead to interruption or discontinuation of study drug. Final results from 96 weeks of treatment in open-label extension Study 112 evaluating subjects aged 2 years and older showed 1 (1.4%) subject had an AE of cataract subcapsular during the treatment-emergent period, which was not reported as clinically significant. The event was mild in severity, non-serious, and did not require treatment or lead to change in study drug dosing.

In the 24-week, placebo-controlled Study 124 in CF subjects aged 6 years and older with a non-*F508del* ELX/TEZ/IVA-responsive *CFTR* mutation, there were no subjects with AEs of cataract or lens opacities.

**Risk factors and risk groups**
Risk factors for cataracts include aging, trauma, UV light and radiation exposure, diabetes mellitus, intraocular inflammation, and corticosteroid use.[65-68]

**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 IVA treatment and cataract development or progression, although a contributing role cannot be completely excluded given the nonclinical finding. 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 ELX/TEZ/IVA.

The potential effect on cataracts is described in the product information, including a recommendation for baseline and follow-up ophthalmological examinations 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 anticipated.

### *SVII.3.3 Presentation of the Missing Information*

#### *SVII.3.3.1 Missing Information – Use in Pregnant and Lactating Women*

**Evidence source**
Nonclinical studies indicated that ELX, TEZ, and IVA are not teratogens. Additional nonclinical studies showed ELX, TEZ, and IVA were transferred to the placenta of pregnant rats and excreted into the milk of lactating rats.

The effect of ELX/TEZ/IVA on pregnancy and lactation in humans is not known as no clinical studies in pregnant or lactating women have been conducted.

**Population in need of further characterisation**
The safety of ELX/TEZ/IVA treatment in pregnant and lactating women will be further characterised in the post-authorisation setting.

#### *SVII.3.3.2 Missing Information – Long-term Safety*

**Evidence source**
The longest clinical study experience with ELX/TEZ/IVA treatment is approximately 216 weeks.

**Population in need of further characterisation**
Long-term safety of ELX/TEZ/IVA treatment remains under ongoing evaluation in clinical studies and post-authorisation surveillance.

**Characterization of the risk**

Final results from 192 weeks of treatment in the long-term extension Study 105 showed that ELX/TEZ/IVA was generally safe and well tolerated in subjects aged 12 years and older. The safety profile was consistent with that of the parent studies 102/103 and with the established safety profile of ELX/TEZ/IVA; no new safety concerns were identified.

Final results from 192 weeks of treatment in the long-term extension Study 107 (subjects aged 6 years and older) showed that ELX/TEZ/IVA was generally safe and well tolerated. The safety profile was consistent with that of the parent Study 106 and with the established safety profile of ELX/TEZ/IVA; no new safety concerns were identified.

Final results from 96 weeks of treatment in the long-term extension Study 112 (subjects aged 2 years and older) showed that ELX/TEZ/IVA was generally safe and well tolerated. The safety profile was consistent with that of the parent Study 111 Part B and with the established safety profile of ELX/TEZ/IVA; no new safety concerns were identified.

### *SVII.3.3.3 Missing Information – Use in Patients With Moderate or Severe Hepatic Impairment*

**Evidence source**
A dedicated study (Study 007) has been conducted to evaluate the safety and PK of ELX/TEZ/IVA in 11 subjects without CF who have moderate hepatic impairment. Based on the final results from this study, the mean $AUC_{\tau}$ for total ELX increased 1.25-fold, while $C_{max}$ was similar in subjects with moderate hepatic impairment relative to 11 matched healthy subjects. Mean exposures ($AUC_{\tau}$ and $C_{max}$) of total M23-ELX increased approximately 1.7-fold in subjects with moderate hepatic impairment relative to matched healthy subjects. Mean $AUC_{\tau}$ for total ELX+M23-ELX increased 1.36-fold, while $C_{max}$ increased 1.24-fold in subjects with moderate hepatic impairment relative to matched healthy subjects. The exposures of TEZ, IVA and their respective metabolites were generally consistent with studies conducted previously. Overall, ELX/TEZ/IVA administered for 10 days was generally safe and well tolerated in subjects with moderate hepatic impairment and matched healthy subjects.

In the controlled, Phase 3 studies (Studies 102 and 103) and the open-label extension study (Study 105) in CF subjects 12 years of age and older, 12 subjects with a medical history of portal hypertension, hepatic cirrhosis, and/or portal/hepatic fibrosis received ELX/TEZ/IVA treatment. The safety data in these 12 subjects were generally consistent with the safety data in other subjects treated with ELX/TEZ/IVA.

**Population in need of further characterisation**
Overall, the safety experience in patients with moderate or severe hepatic impairment is limited; therefore, the use of ELX/TEZ/IVA in this population is considered missing information.

### *SVII.3.3.4 Missing Information – Use in Children Aged 2 to 11 Years*

**Evidence source**

In the 24-week, uncontrolled Phase 3 Study 106 Part B in subjects aged 6 through 11 years of age, and Study 111 Part B in subjects aged 2 through 5 years of age, treatment with ELX/TEZ/IVA was generally safe and well-tolerated, and the safety results were consistent with the known safety profile. However, the studies had a relatively small sample size (66 subjects in Study 106 Part B, and 75 subjects in Study 111 Part B), and the overall safety experience is still limited. Therefore, the safety of ELX/TEZ/IVA in this age group will need further characterization.

**Population in need of further characterisation**

Safety of ELX/TEZ/IVA treatment in children aged 2 to 11 years remains under ongoing evaluation in clinical studies and post-authorisation surveillance.

**Characterization of the risk**

Final results from 192 weeks of treatment in the long-term extension Study 107 (subjects aged 6 years and older) showed that ELX/TEZ/IVA was generally safe and well tolerated. The safety profile was consistent with that of the parent Study 106 and with the established safety profile of ELX/TEZ/IVA; no new safety concerns were identified.

Final results from 96 weeks of treatment in the long-term extension Study 112 (subjects aged 2 years and older) showed that ELX/TEZ/IVA was generally safe and well tolerated. The safety profile was consistent with that of the parent Study 111 Part B and with the established safety profile of ELX/TEZ/IVA; no new safety concerns were identified.

# SVIII Summary of Safety Concerns

| | |
|---|---|
| **Important identified risks** | • Susceptibility for influenza virus infections<br>• Hepatotoxicity |
| **Important potential risks** | • Cataract |
| **Missing information** | • Use in pregnant and lactating women<br>• Long-term safety<br>• Use in patients with moderate or severe hepatic impairment<br>• Use in children aged 2 to 11 years |

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

## III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaire for use in pregnant or lactating women:

  The purpose of this questionnaire is to obtain structured information on the use of ELX/TEZ/IVA in pregnant and lactating women in the post-authorisation setting. Additionally, information regarding infant ophthalmologic examination findings is requested to further evaluate the important potential risk of cataracts. A copy of the questionnaire is provided in Annex 4.

## III.2 Additional Pharmacovigilance Activities

***III.2.1 Post-authorisation safety study*** is a longitudinal, registry-based study evaluating the real-word effects and utilisation patterns of ELX/TEZ/IVA treatment in CF patients.

**Rationale and study objectives**

- To evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-word setting
- Safety concerns evaluated include:
  - Susceptibility for influenza virus infections
  - Hepatotoxicity
  - Use in patients with moderate or severe hepatic impairment
  - Use in pregnant women
  - Long-term safety
  - Use in children aged 2 to 11 years

**Study design:** Post-authorisation, longitudinal, safety study using data collected by existing national CF patient registries in the EU and US

**Study population:** CF patients who have a record of treatment with ELX/TEZ/IVA in the existing CF patient registries, regardless of age or genotype

**Milestones:** Annual Reports: 31 December 2021/2022/2023/2024;
Final Report: December 2025

***III.2.3 Open-label extension study*** *(Study 125)* is a Phase 3, open-label study evaluating the long-term safety and efficacy of ELX/TEZ/IVA for 96 weeks in CF subjects with non-*F508del CFTR* genotypes.

**Rationale and study objectives**

- To evaluate the long-term safety, tolerability, efficacy, and PD of ELX/TEZ/IVA treatment in CF subjects without *F508del* mutation
- Safety concerns evaluated include:
  - Susceptibility for influenza virus infections
  - Hepatotoxicity
  - Cataract
  - Long-term safety
  - Use in children aged 2 to 11 years

**Study design:** Phase 3, multicenter, open-label extension study for subjects who completed the treatment period in the parent study (VX21-445-124).

**Study population:** Male and female CF subjects 6 years of age and older with at least 1 non-F508del ELX/TEZ/IVA-responsive CFTR mutation.

**Milestones:** Final Report: 31 December 2025

## III.3 Summary Table of Additional Pharmacovigilance Activities

**Table 10 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 which are Conditions of the MA (key to benefit risk)** | | | | |
| Not applicable | | | | |
| **Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)** | | | | |
| Not applicable | | | | |
| **Category 3 – Required additional PV activities (by the competent authority)** | | | | |
| PASS<br><br>Ongoing | Evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting | • Susceptibility for influenza virus infections<br>• Hepatotoxicity<br>• Use in patients with moderate or severe hepatic impairment<br>• Use in pregnant women<br>• Long-term safety<br>• Use in children aged 2 to 11 years | Annual Reports<br><br>Final Report | 31 December 2021/2022/ 2023/2024<br><br>31 December 2025 |
| Open-label extension study (Study 125)<br><br>Ongoing | Evaluate the long-term safety, tolerability, efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in CF subjects without *F508del* mutation | • Susceptibility for influenza virus infections<br>• Hepatotoxicity<br>• Cataract<br>• Long-term safety<br>• Use in children aged 2 to 11 years | Final Report | 31 December 2025 |

CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; *F508del*: an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein; MA: market authorisation; PASS: post-authorisation safety study; PV: pharmacovigilance; Study 125: VX21-445-125

# PART IV Plans for Post-authorisation Efficacy Studies

| Study/Status | Summary of Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Efficacy studies which are conditions of the MA** | | | | |

| Study/Status | Summary of Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| Post-Authorisation Efficacy Study (PAES) (Study Number 131)<br><br>Planned | To evaluate disease progression among children with CF who are heterozygous for *F508del* and are aged 2 through 5 years at the time of ELX/TEZ/IVA initiation | Long-term efficacy among children with CF who are heterozygous for *F508del* and aged 2 through 5 years at the time of ELX/TEZ/IVA initiation | Protocol Submission | 30 June 2024 |
| | | | Final Study Report | 31 December 2029 |
| **Efficacy studies which 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; MA: marketing authorisation; PAES: Post-Authorisation Efficacy Study

# PART V Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

## V.1 Routine Risk Minimisation Measures

**Table 11 Routine Risk Minimisation Measures**

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| **Susceptibility for influenza virus infections** | **Routine risk communication:**<br>SmPC Section 4.8<br>PL Section 4 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>None |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Hepatotoxicity** | **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>Recommendations for LFT monitoring and treatment stopping rules are provided in SmPC Section 4.4.<br>Liver damage and worsening of liver function in people with severe liver disease is discussed in PL Section 4.<br>What to expect for LFT monitoring and how to detect potential signs of liver problems are discussed in PL Sections 2 and 4. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Cataract** | **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 provided in SmPC Section 4.4.<br>Expectations for eye examinations are discussed in PL Section 2. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |

**Table 11 Routine Risk Minimisation Measures**

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| **Use in pregnant and lactating women** | **Routine risk communication:**<br>SmPC Sections 4.6 and 5.3<br>PL Section 2 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>Advice is given regarding use during pregnancy and breastfeeding in SmPC Section 4.6.<br>Advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding in PL Section 2. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Long-term safety** | **Routine risk communication:**<br>SmPC Section 4.8 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>None |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Use in patients with moderate or severe hepatic impairment** | **Routine risk communication:**<br>SmPC Sections 4.2, 4.4, and 5.2<br>PL Sections 2 and 3 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>Recommendations regarding use in patients with hepatic impairment are provided in SmPC Sections 4.2 and 4.4.<br>Advice to speak with a healthcare professional before use in patients with liver problems is provided in PL Sections 2 and 3. |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |
| **Use in children aged 2 to 11 years** | **Routine risk communication:**<br>SmPC Sections 4.1, 4.2, and 4.4<br>PL Sections 1 and 2 |
| | **Routine risk minimisation activities recommending specific clinical measure to address the risk:**<br>None |
| | **Other routine risk minimisation measures beyond the Product Information:**<br>Prescription only |

LFT: liver function test; PL: Package Leaflet; 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

**Table 12 Summary of Risk Minimisation Measures**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Susceptibility for influenza virus infections** | **Routine risk minimisation measures:**<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>• PASS<br>(Annual Reports:<br>31 December 2021/2022/2023/2024; Final Report: 31 December 2025)<br>• Open-label extension study (Study 125)<br>(Final Report: 31 December 2025) |
| **Hepatotoxicity** | **Routine risk minimisation measures:**<br>SmPC Sections 4.4 and 4.8<br>SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided.<br>PL Sections 2 and 4<br>PL Sections 2 and 4 where liver damage and worsening of liver function in patients with severe liver disease, expectations for LFT monitoring and detection of potential signs of liver problems are discussed.<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>• PASS<br>(Annual Reports:<br>31 December 2021/2022/2023/2024; Final Report: 31 December 2025)<br>• Open-label extension study (Study 125)<br>(Final Report: 31 December 2025) |
| **Cataract** | **Routine risk minimisation measures:**<br>SmPC Sections 4.4 and 5.3<br>SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided.<br>PL Section 2<br>PL Section 2 where expectations for eye examinations are discussed.<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>• Open-label extension study (Study 125)<br>(Final Report: 31 December 2025) |
| **Use in pregnant and lactating women** | **Routine risk minimisation measures:**<br>SmPC Sections 4.6 and 5.3<br>SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding.<br>PL Section 2<br>PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding.<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 questionnaire<br><br>**Additional PV activities:**<br>• PASS<br>(Annual Reports:<br>31 December 2021/2022/2023/2024; Final Report: 31 December 2025) |

**Table 12 Summary of Risk Minimisation Measures**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Long-term safety** | **Routine risk minimisation measures:**<br>SmPC Section 4.8<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>• PASS<br>(Annual Reports:<br>31 December 2021/2022/2023/2024; Final Report: 31 December 2025)<br>• Open-label extension study (Study 125)<br>(Final Report: 31 December 2025) |
| **Use in patients with moderate or severe hepatic impairment** | **Routine risk minimisation measure:**<br>SmPC Sections 4.2, 4.4, and 5.2<br>SmPC Sections 4.2 and 4.4 where recommendations regarding use in patients with hepatic impairment are provided.<br>PL Sections 2 and 3<br>PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided.<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>• PASS<br>(Annual Reports:<br>31 December 2021/2022/2023/2024; Final Report: 31 December 2025) |
| **Use in children aged 2 to 11 years** | **Routine risk minimisation measure:**<br>SmPC Sections 4.1, 4.2, and 4.4<br>PL Sections 1 and 2<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>• PASS<br>(Annual Reports:<br>31 December 2021/2022/2023/2024; Final Report: 31 December 2025)<br>• Open-label extension study (Study 125)<br>(Final Report: 31 December 2025) |

LFT: liver function test; PASS: Post-authorisation safety study; PL: Package Leaflet; PV: pharmacovigilance; Q3: Quarter 3; SmPC: Summary of Product Characteristics; Study 112: VX20-445-112; Study 125: VX21-445-125

# PART VI Summary of the RMP

## Summary of Risk Management Plan for KAFTRIO (Elexacaftor in Combination With Tezacaftor and Ivacaftor)

This is a summary of the risk management plan (RMP) for KAFTRIO when used in a combination regimen with ivacaftor tablets or granules. The RMP details important risks of KAFTRIO, how these risks can be minimised, and how more information will be obtained about KAFTRIO's risks and uncertainties (missing information) when used in combination with ivacaftor.

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

This summary of the RMP for KAFTRIO 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 safety concerns or changes to the current ones will be included in updates of KAFTRIO's RMP.

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

KAFTRIO in a combination regimen with ivacaftor is authorised for the treatment of CF in patients aged 2 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data. It contains elexacaftor in combination with tezacaftor and ivacaftor as the active substances and it is given orally.

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

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

Important risks of KAFTRIO when used in combination with ivacaftor, together with measures to minimise such risks and the proposed studies for learning more about KAFTRIO'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.

If important information that may affect the safe use of KAFTRIO in combination with ivacaftor is not yet available, it is listed under 'missing information' below.

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

Important risks of KAFTRIO in combination with ivacaftor 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 KAFTRIO. 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 (e.g., on the long-term use of the medicine).

| **List of important risks and missing information** |
|---|

| | |
|---|---|
| Important identified risks | • Susceptibility for influenza virus infections<br>• Hepatotoxicity |
| Important potential risks | • Cataract |
| Missing information | • Use in pregnant and lactating women<br>• Long-term safety<br>• Use in patients with moderate or severe hepatic impairment<br>• Use in children aged 2 to 11 years |

## *II.B Summary of important risks*

| | |
|---|---|
| **Susceptibility for influenza virus infections (Important identified risk)** | |
| Evidence for linking the risk to the medicine | In the 24-week, placebo-controlled Phase 3 study in CF subjects 12 years of age and older (Study 102), a higher incidence of influenza AEs was reported in the ELX/TEZ/IVA group compared to the placebo group. In the KAFTRIO (ELX/TEZ/IVA) group, all AEs of influenza were mild or moderate in severity and most were non-serious. All subjects continued KAFTRIO (ELX/TEZ/IVA) dosing or resumed treatment after an interruption. In the open-label extension Study 105, the rate of influenza AEs during extended KAFTRIO (ELX/TEZ/IVA) treatment was lower than the rate in the KAFTRIO (ELX/TEZ/IVA) group in Study 102, and similar to the rate in the placebo group in Study 102. The influenza data in subjects 2 through 11 years of age (Studies 106, 107, 111, and 112) and in subjects with non-*F508del* mutations (Study 124) were consistent with those in subjects ≥12 years of age.<br>Based on the overall safety experience with KAFTRIO (ELX/TEZ/IVA), an association between treatment and the susceptibility for influenza cannot be completely excluded. |
| Risk factors and risk groups | Patients who are hospitalised frequently or for long-term durations are at a greater risk for contracting influenza from other infected individuals. Risk factors for influenza-related complications include common CF comorbidities (e.g., chronic lung disease, asthma) and a compromised immune system. |
| Risk minimisation measures | SmPC Sections 4.8<br>PL Section 4<br>Prescription only |
| Additional pharmacovigilance activities | • Post-authorisation safety study<br>• Open-label extension study (Study 125)<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |
| **Hepatotoxicity (Important identified risk)** | |
| Evidence for linking the risk to the medicine | In the 24-week, placebo-controlled, Phase 3 study in CF subjects 12 years of age and older (Study 102), the incidence of elevated transaminase events (AEs or ALT/AST laboratory elevations >3 × ULN) was higher in the group of subjects treated with KAFTRIO (ELX/TEZ/IVA) than in the group of subjects receiving placebo. LFT elevations were also seen in other clinical studies with KAFTRIO (ELX/TEZ/IVA), including the open-label extension study (Study 105). LFT elevations in subjects 2 through 11 years of age (Studies 106, 107, 111, and 112) and in subjects with non-*F508del* mutations (Study 124) were consistent with those in subjects ≥12 years of age.<br>Elevated transaminases with KAFTRIO (ELX/TEZ/IVA) treatment were generally transient and resolved without long-term effects. Very high levels of transaminase elevations or transaminase elevations with concurrent total bilirubin elevation may be a sign of liver injury which could become permanent or be life-threatening. In addition, post-marketing reports of drug-induced liver injury have been received, including cases of liver injury characterized by concurrent elevations of transaminases and bilirubin, and cases of liver failure leading to transplantation in a patients with and without pre-existing advanced liver disease. An association with KAFTRIO (ELX/TEZ/IVA) treatment cannot be excluded in these cases. The overall safety experience with KAFTRIO (ELX/TEZ/IVA) suggests that an association between treatment and hepatotoxicity cannot be excluded. |
| Risk factors and risk groups | Generally known risk factors for increases in transaminases include concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, viral hepatitis), comorbidities (e.g., CF liver disease), and use of concomitant drugs (e.g., acetaminophen, antibiotics) or substances (alcohol) known to be associated with liver enzyme elevations. |
| Risk minimisation measures | SmPC Sections 4.4 and 4.8<br>SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided.<br>PL Sections 2 and 4 |

| | |
|---|---|
| | PL Sections 2 and 4 where liver damage and worsening of liver function in people with severe liver disease, expectations for LFT monitoring and detection of potential signs of liver problems are discussed.<br>Prescription only |
| Additional pharmacovigilance activities | • Post-authorisation safety study<br>• Open-label extension study (Study 125)<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |
| **Cataract (Important potential risk)** | |
| Evidence for linking the risk to the medicine | Cataracts (lens opacities) considered related to IVA treatment were seen during studies in newborn rats but were not observed in older animals or in longer duration animal studies. Given developmental differences between rats and humans, it is unlikely that the cataract finding is relevant to humans 2 years of age and older.<br>Non-congenital cataracts without impact on vision have been reported in paediatric subjects treated with IVA-containing regimens during clinical studies and post-authorisation surveillance, but the relationship of these events to treatment is uncertain due to the presence of other possible causes. |
| Risk factors and risk groups | Risk factors for cataracts include aging, trauma, UV light and radiation exposure, diabetes mellitus, intraocular inflammation, and corticosteroid use. |
| Risk minimisation measures | SmPC Sections 4.4 and 5.3<br>SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided.<br>PL Section 2<br>PL Section 2 where expectations for eye examinations are discussed.<br>Prescription only |
| Additional pharmacovigilance activities | • Open-label extension study (Study 125)<br>See Section II.C this summary for an overview of the post-authorisation development plan. |
| **Use in pregnant and lactating women (Missing information)** | |
| Risk minimisation measures | SmPC Sections 4.6 and 5.3<br>SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding.<br>PL Section 2<br>PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding.<br>Prescription only |
| Additional pharmacovigilance activities | • Post-authorisation safety study<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |
| **Long-term safety (Missing information)** | |
| Risk minimisation measures | SmPC Section 4.8<br>Prescription only |
| Additional pharmacovigilance activities | • Post-authorisation safety study<br>• Open-label extension study (Study 125)<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |
| **Use in patients with moderate or severe hepatic impairment (Missing information)** | |
| Risk minimisation measures | SmPC Sections 4.2, 4.4, and 5.2<br>SmPC Sections 4.2 and 4.4 where recommendations regarding use in patients with hepatic impairment are provided.<br>PL Sections 2 and 3<br>PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided.<br>Prescription only |
| Additional pharmacovigilance activities | • Post-authorisation safety study<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |
| **Use in children aged 2 to 11 years** | |
| Risk minimisation measures | SmPC Sections 4.1, 4.2, and 4.4.<br>PL Sections 1 and 2<br>Prescription only |
| Additional pharmacovigilance activities | • Post-authorisation safety study<br>• Open-label extension study (Study 125) |

See Section II.C of this summary for an overview of the post-authorisation development plan

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor (also known as KAFTRIO); IVA: ivacaftor (a component of KAFTRIO); LFT: liver function test; PL: Package Leaflet; SmPC: Summary of Product Characteristics; Study 125: VX21-445-125; ULN: upper limit of normal; UV: ultraviolet

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

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

The following study is a condition of the marketing authorisation:

**Study Name and Title:** The Post-Authorisation Efficacy study (PAES) is an observational, registry-based study to evaluate disease progression among children with CF who are heterozygous for *F508del* and are aged 2 through 5 years at the time of ELX/TEZ/IVA treatment initiation.

**Rationale and Study Objectives:**

The objective of this study is to evaluate long-term efficacy among children with CF who are heterozygous for *F508del* and aged 2 through 5 years at the time of ELX/TEZ/IVA initiation.

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

**Post-authorisation safety study** *(PASS)*
Purpose of the study: To evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the realworld setting

**Open-label extension study** *(Study 125)*

Purpose of the study: To evaluate the long-term safety, tolerability, efficacy and pharmacodynamics of ELX/TEZ/IVA treatment for 96 weeks in CF subjects without *F508del* mutation in *CFTR* gene.

# 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 form

- **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] or Fax: [redacted] (Telephone: [redacted])

| **Vertex Global Patient Safety Trikafta (Elexacaftor/Tezacaftor/Ivacaftor and Ivacaftor)** | |
|---|---|
| **To:** | , , , |
| **Site Contact:** | Fax: ; Email: |
| **Date:** | 05-JUN-2023 |
| **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 |
| **Was an initial/baseline ophthalmologic examination performed for the infant at or shortly after birth? Yes ___ No ___**<br>**If yes, please provide date of exam, a summary of the findings, and plan for any follow-up:** | | | | | |
| **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):** | | |
| Has the patient denied permission for his/her physician or designee to be contacted? ☐ Yes ☐ No | | |

### 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.*

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

Not applicable.

# REFERENCES


1 Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros. 2008;7(5):450-3.

2 Sanders DB, Fink AK. Background and Epidemiology. Pediatr Clin North Am. 2016;63(4):567-84.

3 Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry: 2017 annual data report. Bethesda. Maryland, USA: Cystic Fibrosis Foundation; 2018.

4 Massie J, Curnow L, Gaffney L, Carlin J, Francis I. Declining prevalence of cystic fibrosis since the introduction of newborn screening. Arch Dis Child. 2010;95(7):531-3.

5 Cystic Fibrosis Canada. Canadian cystic fibrosis patient data registry report 2017. Toronto, Ontario: Cystic Fibrosis Canada; 2018.

6 Ruseckaite R AA, Ranger T, Dean J, Gardam M, Bell S, Burke N on behalf of the Australian Cystic Fibrosis Data Registry. The Australian Cystic Fibrosis Data Registry Annual Report, 2017. Report No 20. Melbourne, Australia Monash University, Department of Epidemiology and Preventive Medicine; 2019.

7 Cystic Fibrosis Foundation. What is cystic fibrosis? [Internet]. Available from: http://www.cff.org/AboutCF/. Accessed 2019.

8 Colombo C, Littlewood J. The implementation of standards of care in Europe: state of the art. J Cyst Fibros. 2011;10(Suppl 2):S7-15.

9 Orphanet. Report Prevalence and incidence of rare diseases: Bibliographic data. Report date: 2019.

10 Statistics Canada. National Database [Internet]. Available from: https://www150.statcan.gc.ca/n1/pub/12-581-x/12-581-x2018000-eng.pdf. Accessed 2020.

11 Australian Bureau of Statistics. National Database [Internet]. Available from: https://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/30125843DE7F366ECA2582570013F5FE?opendocument. Accessed 2020.

12 European Cystic Fibrosis Society Patient Registry. 2017 ECFS Patient Registry annual data report. Karup, Denmark: European Cystic Fibrosis Society; 2019.

13 Cystic Fibrosis Trust. UK Cystic Fibrosis Registry Annual Data Report 2018. Bromley Kent, United Kingdom: Cystic Fibrosis Trust; 2019.

14 Cystic Fibrosis Registry of Ireland. Cystic Fibrosis Registry of Ireland 2017 annual report. Dublin, Ireland: Cystic Fibrosis Registry of Ireland; 2019.

15 French Cystic Fibrosis Registry. Annual Data Report 2016. Paris, France: Vaincre la Mucoviscidose and Institut National d'Etudes Demographiques; 2018.

16 MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation patient registry. Ann Intern Med. 2014;161(4):233-41.

17 Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. Eur Respir J. 2015;45(3):670-9.

18 Hodson ME, Simmonds NJ, Warwick WJ, Tullis E, Castellani C, Assael B, et al. An international/multicentre report on patients with cystic fibrosis (CF) over the age of 40 years. J Cyst Fibros. 2008;7(6):537-42.

19 Mehta G, Macek M, Jr., Mehta A, European Registry Working G. Cystic fibrosis across Europe: EuroCareCF analysis of demographic data from 35 countries. J Cyst Fibros. 2010;9(Suppl 2):S5-S21.

20 Hamosh A, FitzSimmons SC, Macek M, Jr., Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr. 1998;132(2):255-9.

21 Stern RC, Borkat G, Hirschfeld SS, Boat TF, Matthews LW, Liebman J, et al. Heart failure in cystic fibrosis. Treatment and prognosis of cor pulmonale with failure of the right side of the heart. Am J Dis Child. 1980;134(3):267-72.

22 Mukoviszidose EV. Deutsches mukoviszidose-register berichtsband 2016. Bonn, Germany: Mukoviszidose Institut. 2017;

23 Maffessanti M, Candusso M, Brizzi F, Piovesana F. Cystic fibrosis in children: HRCT findings and distribution of disease. J Thorac Imaging. 1996;11(1):27-38.

24 de Jong PA, Ottink MD, Robben SG, Lequin MH, Hop WC, Hendriks JJ, et al. Pulmonary disease assessment in cystic fibrosis: comparison of CT scoring systems and value of bronchial and arterial dimension measurements. Radiology. 2004;231(2):434-9.

25 Helbich TH, Heinz-Peer G, Eichler I, Wunderbaldinger P, Götz M, Wojnarowski C, et al. Cystic fibrosis: CT assessment of lung involvement in children and adults. Radiology. 1999;213(2):537-44.

26 Navarro J, Rainisio M, Harms HK, Hodson ME, Koch C, Mastella G, et al. Factors associated with poor pulmonary function: cross-sectional analysis of data from the ERCF. European Epidemiologic Registry of Cystic Fibrosis. Eur Respir J. 2001;18(2):298-305.

27 Leeuwen L, Magoffin AK, Fitzgerald DA, Cipolli M, Gaskin KJ. Cholestasis and meconium ileus in infants with cystic fibrosis and their clinical outcomes. Arch Dis Child. 2014;99(5):443-7.

28 Borowitz D, Gelfond D. Intestinal complications of cystic fibrosis. Curr Opin Pulm Med. 2013;19(6):676-80.

29 Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. J Pediatr Gastroenterol Nutr. 1999;28(Suppl 1):S1-13.

30 Colombo C. Liver disease in cystic fibrosis. Curr Opin Pulm Med. 2007;13(6):529-36.

31 Bhardwaj S, Canlas K, Kahi C, Temkit M, Molleston J, Ober M, et al. Hepatobiliary abnormalities and disease in cystic fibrosis: epidemiology and outcomes through adulthood. J Clin Gastroenterol. 2009;43(9):858-64.

32 Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology. 2002;36(6):1374-82.

33 Wilschanski M, Rivlin J, Cohen S, Augarten A, Blau H, Aviram M, et al. Clinical and genetic risk factors for cystic fibrosis-related liver disease. Pediatrics. 1999;103(1):52-7.

34 Lamireau T, Monnereau S, Martin S, Marcotte JE, Winnock M, Alvarez F. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol. 2004;41(6):920-5.

35 Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology. 1999;30(5):1151-8.

36 Mayer-Hamblett N, Kloster M, Ramsey BW, Narkewicz MR, Saiman L, Goss CH. Incidence and clinical significance of elevated liver function tests in cystic fibrosis clinical trials. Contemp Clin Trials. 2013;34(2):232-8.

37 Woodruff S, Sontag M, Accurso F, Sokol RJ, Narkewicz M. Prevalence of elevated liver function tests in children with cystic fibrosis diagnosed by newborn screen. J Pediatr Gastroenterol Nutr. 2007;45(4):E27-8.

38 Corbett K, Kelleher S, Rowland M, Daly L, Drumm B, Canny G, et al. Cystic fibrosis-associated liver disease: a population-based study. J Pediatr. 2004;145(3):327-32.

39 Cystic Fibrosis Registry of Ireland. Cystic Fibrosis Registry of Ireland 2014 annual report. Dublin, Ireland: Cystic Fibrosis Registry of Ireland; 2015.

40 Rowland M, Gallagher CG, O'Laoide R, Canny G, Broderick A, Hayes R, et al. Outcome in cystic fibrosis liver disease. Am J Gastroenterol. 2011;106(1):104-9.

41 van den Berg JM, Kouwenberg JM, Heijerman HG. Demographics of glucose metabolism in cystic fibrosis. J Cyst Fibros. 2009;8(4):276-9.

42 Georgiopoulou VV, Denker A, Bishop KL, Brown JM, Hirsh B, Wolfenden L, et al. Metabolic abnormalities in adults with cystic fibrosis. Respirology. 2010;15(5):823-9.

43 Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32(9):1626-31.

44 Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: five year prospective study. BMJ. 1995;311(7006):655-9.

45 Adler AI, Shine BS, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. Diabetes Care. 2008;31(9):1789-94.

46 Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153(4):345-52.

47 Chamnan P, Shine BS, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. Diabetes Care. 2010;33(2):311-6.

48 Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J, et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. Am J Respir Crit Care Med. 2015;191(2):194-200.

49 Botton E, Saraux A, Laselve H, Jousse S, Le Goff P. Musculoskeletal manifestations in cystic fibrosis. Joint Bone Spine. 2003;70(5):327-35.

50 Aris RM, Renner JB, Winders AD, Buell HE, Riggs DB, Lester GE, et al. Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Intern Med. 1998;128(3):186-93.

51 Henderson RC, Madsen CD. Bone density in children and adolescents with cystic fibrosis. J Pediatr. 1996;128(1):28-34.

52 Henderson RC, Madsen CD. Bone mineral content and body composition in children and young adults with cystic fibrosis. Pediatr Pulmonol. 1999;27(2):80-4.

53 Stead RJ, Houlder S, Agnew J, Thomas M, Hodson ME, Batten JC, et al. Vitamin D and parathyroid hormone and bone mineralisation in adults with cystic fibrosis. Thorax. 1988;43(3):190-4.

54 Paccou J, Zeboulon N, Combescure C, Gossec L, Cortet B. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int. 2010;86(1):1-7.

55 Farrell PM, Kosorok MR, Laxova A, Shen G, Koscik RE, Bruns WT, et al. Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. N Engl J Med. 1997;337(14):963-9.

56 Durno C, Corey M, Zielenski J, Tullis E, Tsui LC, Durie P. Genotype and phenotype correlations in patients with cystic fibrosis and pancreatitis. Gastroenterology. 2002;123(6):1857-64.

57 Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui LC, et al. Genetic determination of exocrine pancreatic function in cystic fibrosis. Am J Hum Genet. 1992;50(6):1178-84.

58 Simmonds NJ, Cullinan P, Hodson ME. Growing old with cystic fibrosis - the characteristics of long-term survivors of cystic fibrosis. Respir Med. 2009;103(4):629-35.

59 Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Solé A, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. Thorax. 2014;69(12):1090-7.

60 Organization WH. Chronic cor pulmonale: report of an expert committee. . Circulation. 1963;27(4):594-615.

61 Bright-Thomas RJ, Webb AK. The heart in cystic fibrosis. J R Soc Med. 2002;95(Suppl 41):2-10.

62 Perrin FM, Serino W. Ischaemic heart disease--a new issue in cystic fibrosis? J R Soc Med. 2010;103(Suppl 1):S44-8.

63 Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States - 2018-2019 influenza season [Internet]. Available from: https://www.cdc.gov/flu/about/burden/2018-2019.html. Accessed 11 June 2020.

64 Tokars JI, Olsen SJ, Reed C. Seasonal Incidence of Symptomatic Influenza in the United States. Clin Infect Dis. 2018;66(10):1511-18.

65 Javitt JC, Wang F, West SK. Blindness due to cataract: epidemiology and prevention. Annu Rev Public Health. 1996;17(-):159-77.

66 Leske MC, Chylack LT, Jr., Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. Arch Ophthalmol. 1991;109(2):244-51.

67 Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors: the Visual Impairment Project. Arch Ophthalmol. 2006;124(1):79-85.

68 Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med. 1997;337(1):8-14.