Module 1.8.2

EU RISK MANAGEMENT PLAN

For ALYFTREK (vanzacaftor in combination with tezacaftor and deutivacaftor)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ADME	absorption, distribution, metabolism, and excretion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BMI	body mass index
CF	cystic fibrosis
CFRD	CF-related diabetes
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
D-IVA	Deutivacaftor
ECFSPR	European CF Society Patient Registry
ECG	Electrocardiogram
EEA	European Economic Area
EFD	embryo fetal development
ELX	Elexacaftor
ELX/TEZ/IVA	elexacaftor/tezacaftor/ivacaftor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
F508del	*CFTR* in-frame mutation that results in an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein
F	*F508del mutation*
F/F	F508del/F508del genotype
F/G	F508del/gating genotypes
F/MF	F508del/minimal function genotypes
F/RF	F508del/residual function genotypes
FEED	fertility and early embryonic development
FRT	fischer rat thyroid
IV	Intravenous
IVA	Ivacaftor
LFT	liver function test
N	number of subjects
n/a	not available
NOAEL	no-observed-adverse-effect level
PAES	post-authorisation efficacy study
PK	pharmacokinetic(s)
PL	Patient Leaflet
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PPND	pre- and post-natal development
PY	person year, patient year
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
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SwCl	sweat chloride
TC	triple combination
TCR	triple combination responsive
TEZ	Tezacaftor
TEZ/IVA	TEZ in combination with IVA
UK	United Kingdom
ULN	upper limit of normal
US	United States
VNZ	Vanzacaftor
VNZ/TEZ/D-IVA	vanzacaftor/tezacaftor/deutivacaftor

PART I Product(s) Overview

Active substance(s)	ALYFTREK **(vanzacaftor/tezacaftor/deutivacaftor [VNZ/TEZ/D-IVA])**
Pharmacotherapeutic group(s) (ATC Code)	Other respiratory system products (R07AX33)
Market Authorisation Applicant	Vertex Pharmaceuticals (Ireland) Limited
Medicinal products to which this RMP refers	VNZ/TEZ/D-IVA
Invented name(s) in the European Economic Area (EEA)	ALYFTREK
Market authorisation procedure	centralised
Brief description of the product	VNZ is 13*H*-17,20-Methano-8,12-nitrilo-12*H*-pyrido[3,2-*d*][1,2,6,13]thiatriazacyclooctadecin-5(6*H*)-one, 2-[3-(2-dispiro[2.0.2.1]hept-7-ylethoxy)-1*H*-pyrazol-1-yl]-14,15,16,17,18,19-hexahydro-19,19-dimethyl-,7,7-dioxide, (17*S*) TEZ is 1-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1*H*-indol-5-yl}cyclopropane-1-carboxamide D-IVA is *N*-(2-(*tert*-butyl)-5-hydroxy-4-(2-(methyl-d_3)propan-2-yl-1,1,1,3,3,3-d_6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
	VNZ is a next-generation cystic fibrosis transmembrane conductance regulator (CFTR) corrector facilitates that cellular processing and trafficking of select mutant forms that can cause defects throughout the CFTR protein (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface, resulting in increased chloride transport. The effect of TEZ (another CFTR corrector) administered in combination with VNZ has an additive effect in facilitating the cellular processing and trafficking of select mutant forms that can cause defects throughout the CFTR protein (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. D-IVA is a deuterated isotopolog of ivacaftor (IVA), a CFTR potentiator that increases the channel open probability (or gating) of CFTR at the cell surface to enhance chloride transport. All 3 binding sites are located away from the site of the defect in F508del-CFTR protein or other VNZ/TEZ/D-IVA responsive CF transmembrane conductance regulator gene (*CFTR)* mutations that are important for protein stability and/or function. The combined allosteric effect of VNZ, TEZ, and D-IVA is increased quantity and function of CFTR at the cell surface, which results in increased CFTR activity as measured by CFTR-mediated chloride transport.
Hyperlink to the Product Information	(Proposed) Summary of Product Characteristics for ALYFTREK
Indication(s) in the EEA	**Current (if applicable):** Not applicable
	Proposed (if applicable): ALYFTREK is indicated in a combination regimen for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-Class I mutation in the *CFTR* gene.
Dosage in the EEA	**Current (if applicable):** Not applicable
	Proposed: **For patients 6 years of age and older weighing ≥40 kg**: The recommended dose is 2 tablets (each containing 10 mg VNZ, 50 mg TEZ, and 125 mg D-IVA) taken orally once a day (total daily dose: 20 mg VNZ, 100 mg TEZ, 250 mg D-IVA). **For patients aged 6 years of age and older weighing <40 kg**: The recommended dose is 3 tablets (each containing 4 mg VNZ, 20 mg TEZ, and 50 mg D-IVA) taken orally once a day (total daily dose: 12 mg VNZ, 60 mg TEZ, and 150 mg D-IVA).
Pharmaceutical form(s) and strengths	**Current (if applicable):** Not applicable
	Proposed: **VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg tablets:** Each film coated tablet contains VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg as a fixed-dose combination tablet, which is purple, capsule-shaped tablet debossed with "V10" on one side and plain on the other (15 mm × 7 mm). **VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg tablets:** Each film coated tablet contains VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg as a fixed-dose combination

	tablet, which is purple, round-shaped tablet debossed with "V4" on one side and plain on the other (7.35 mm diameter).
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 ALYFTREK (vanzacaftor in combination with tezacaftor and deutivacaftor [VNZ/TEZ/D-IVA]) is people with CF aged 6 years and older who have at least one non-Class I mutation in the *CFTR* gene.

SI.1 Incidence

The incidence of CF varies markedly across populations and within each country based on factors such as ethnicity.[1-3]

Europe: CF incidence rate estimates based on 2019 newborn screening data from 26 countries in Europe ranged from 1 in 1,808 live births in Luxembourg to 1 in 10,928 live births in Portugal.[2]

North America: As of 2019, the estimated incidence rate of CF was 1 in 5,130 live births in the United States and 1 in 3,848 live births in Canada.[3]

Australia: Approximately 1 in 3,650 children in Australia were born with CF in 2015.[4]

SI.2 Prevalence

General CF Population

There are approximately 92,000 people with CF in the CF registries of Europe, US, Canada, and Australia.

Europe: In 2021, there were 51,168 people with CF living in Europe and neighbouring countries seen annually in the European CF Society Patient Registry (ECFSPR).[5]

US: In the US, in 2022, there were 32,621 people with CF in the US CF Foundation patient registry and an overall prevalence of 0.98 per 10,000 people.[6, 7]

Canada: In Canada, in 2021, there were 4,338 people with CF in the Canadian CF Registry and an overall prevalence of 1.17 per 10,000 people.[8, 9]

Australia: In Australia, in 2021, there were 3,616 people with CF in the Australian CF Data Registry and an overall prevalence of 1.42 per 10,000 people.[10, 11]

Target Population

Europe: Based on the 2021 annual data report from the ECFSPR that included data on 51,158 people with CF from 40 countries throughout Europe and neighbouring countries, 99.4% of the patients in the registry had been genotyped. Of those patients with available genotype data and who were seen in 2021, 80.3% had at least one *F508del-CFTR* allele.[5]

US: Based on the 2022 report from the US CF Foundation patient registry that included data on 32,621 people with CF, 99.4% of the patients in the registry had been genotyped. Of those with available genotype data, 85.4% had at least one *F508del-CFTR* allele.[6]

Canada: Based on the 2021 report from the Canadian CF registry that included data on 4,338 people with CF, 99.1% of the patients in the registry had been genotyped. Of those with available genotype data, 86.8% had at least one *F508del-CFTR* allele.[8]

Australia: Based on the 2021 report from the Australian CF registry that included data on 3,616 people with CF, 98.4% of the patients in the registry had been genotyped. Of those with available genotype data, 90.0% had at least one *F508del-CFTR* allele.[10]

These estimates account for individuals with at least one *F508del-CFTR* allele, which represents the majority of the indicated population. Additional people with CF will be indicated on the basis of having another responsive allele.

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 have 2 copies of the defective *CF transmembrane conductance regulator (CFTR)* gene (1 copy from each parent) that lead to no or 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 months in 2021, as reported by the CF registries in UK, Ireland, and France.[12-14] Across 40 countries that contributed data to ECFSPR in 2021, the median age at diagnosis was 3.6 months.[5]

Similarly, in the US, the median age at diagnosis was 3 months according to a 2022 registry report.[6]

In Canada, newborn screening is performed in all provinces (Quebec added CF testing to their newborn screening in 2018). In 2021, the majority (68.4%) of individuals with new diagnoses of CF were identified through newborn screening. Likewise, the majority of all people in the registry (60.5%) were diagnosed by 1 year of age.[8]

Age distribution among prevalent patients

Among the people with CF in the ECFSPR alive at the end of 2021, 54.0% were aged 18 years and older and the median age was 19.8 years.[5]

In the US in 2022, 58.3% of people with CF were aged 18 years and older and the median age was 21.9 years.[6]

In Canada in 2021, 65.0% of people with CF were 18 years and older and the median age was 25.3 years.[8]

In Australia in 2021, 55.8% of people with CF were aged 18 years and older and the median age was 20.6 years.[10]

Sex

Among children with CF in Europe, a male preponderance exists at birth and persists and is reflected at all ages.[15]

In the ECFSPR 2021 annual report, 52.3% of people with CF were males.[5]

In the US 2022 annual registry report, 51.7% of people with CF were males.[6]

In the Canada 2021 annual registry report, 53.3% of people with CF were males.[8]

In the Australian 2021 annual registry report, 52.8% of people with CF were males.[10]

Race / ethnic origin

CF affects all racial and ethnic groups, but is most common among Caucasians. Among people with CF in the US in 2022, 91.2% were whites, 3.5% African Americans, and 5.3% other races, with 10.0% being identified as Hispanic (any race) (races are not mutually exclusive as recorded in the US CF Foundation Patient Registry).[6]

SI.4 Main Existing Treatment Options

Current treatments for CF include therapies addressing the consequences of CF disease (e.g., antibiotics and mucolytics) and CFTR modulators (i.e., correctors and potentiators), which address the underlying cause of CF.

Highly effective CFTR modulators represent a major advancement in the treatment of CF because they target the underlying cause of CF by improving CFTR function, resulting in lower sweat chloride (SwCl) levels. The first highly effective CFTR modulator therapy approved was Kalydeco™ (IVA) in 2012, which provided significant improvements in CFTR function but was indicated for only a small proportion of people with CF (~4-5%) who had a G551D mutation. The approvals of the dual combination therapies, Orkambi™ (lumacaftor/IVA; in 2015) and Symdeko/Symkevi™ (TEZ/IVA; in 2018) provided treatment options for approximately 50% of people with CF (including the most common CFTR genotype, homozygous for *F508del*; F/F); however, these therapies only brought a small proportion of people with CF to below the CF diagnostic threshold (SwCl <60 mmol/L) and to normal SwCl levels (<30 mmol/L). The triple combination (TC) regimen, Trikafta/Kaftrio™ (ELX/TEZ/IVA; in 2019), was an important step forward in the treatment of CF, as it is a treatment option for approximately 90% of people with CF and provided significant improvements in CFTR function. However, although Trikafta/Kaftrio was an improvement over dual therapies, it still leaves a large portion of pwCF with abnormal levels of CFTR function (as measured by sweat chloride).

In addition to CFTR modulators, the main existing treatment options for CF comprise drugs or physiotherapy for the individual organ-specific disease manifestations or comorbidities of CF, which may encompass the following:

Disease Manifestation / Comorbidity	Treatment Options
CF lung disease	• Airway hydration (hypertonic saline nebulisation) • Mucolytics (dornase alfa) • Oral antibiotics (amoxicillin clavulanate, ciprofloxacin, azithromycin, clarithromycin) • Inhaled antibiotics (tobramycin, aztreonam, colistin) • IV antibiotics (ceftazidime, meropenem, piperacillin-tazobactam, tobramycin, amikacin) • Bronchodilators (albuterol, salmeterol) • Oxygen • Inhaled corticosteroids (budesonide, fluticasone) • Systemic corticosteroids (prednisolone, prednisone) • Chest physiotherapy
CF liver disease	• Oral bile acid therapy (ursodeoxycholic acid)
CFRD	• Insulin
CF-related osteoporosis and osteopenia	• Vitamin D and calcium supplementation
Gastrointestinal complications	• Laxative treatment (polyethylene glycol) • Pancreatic enzyme replacement • Acid reduction therapy (H2-blockers; proton-pump inhibitors) • Supplementation of fat-soluble vitamins (A, D, E, and K) and zinc

	• Appetite stimulation (hydroxyzine, cyproheptadine, megestrol acetate, dronabinol) • Supplemental feeding (tube feeding)

CF: cystic fibrosis; CFRD: CF-related diabetes; IV: intravenous

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

Mortality

Prior to recent advances in CF care, including CFTR modulator treatment for patients with responsive mutations, EuroCare CF reported median age at death for 14 European countries varied between 9.5 years in Macedonia and 33.0 years in the Netherlands.[16]

In 2010, a patient with CF born in the last 2 decades of the 20th century (in an economically developed nation) was expected to have a greater than 50% chance of survival to 40 years of age.[15] 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%.[17]

There have been substantial improvements in the survival of people with CF in recent years. The reported median age at death, median predicted survival, and mortality rates in 2021 or 2022 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
Australia, 2021[10]	36.8	56.9	0.5%
Canada, 2021[8]	38.7	57.3	1.0%
France, 2021[14]	37.8	n/a	0.6%
Germany, 2021[17]	42	54.3	0.6%
Ireland, 2021[18]	33	51.8	0.8%
UK, 2021[13]	38	53.3	0.6%
US, 2022[6]	36.6	56.6	0.7%

UK: United Kingdom; US: United States

Morbidity

CF is a systemic, multiorgan disease. The most affected organs are lungs, pancreas, liver/gallbladder, intestines, sinuses, vas deferens, secretory glands, and bones. Other complications and comorbidities of CF include mental health comorbidities, heart failure, and CF-related arthropathy.

The multisystem manifestations of CF stem from decreased CFTR protein activity and reduced chloride ion transport.[19-21] Defective CFTR activity hinders chloride absorption, resulting in higher-than-normal chloride concentrations in sweat reaching the skin surface.[22] SwCl is a reliable biomarker for CF diagnosis, with ≥60 mmol/L being the threshold for CF diagnosis and <30 mmol/L being the threshold at which CF diagnosis is unlikely.[23, 24] A registry-based analysis of 25,753 people with CF showed that elevated SwCl concentration at diagnosis may be associated with both mortality and future lung function and nutritional outcomes.[25]

Availability of highly effective CFTR modulator therapies lead to dramatic improvements in patient survival. As people with CF are living longer lives, they are expected to face new challenges of managing similar comorbidities affecting the average aging population including, but not limited to cardiovascular disease, dyslipidemia, diabetes, obesity,

pulmonary hypertension, obstructive sleep apnea, liver disease, bone disease, and malignancy.[26, 27]

SI.6 Important Comorbidities and Complications

The important comorbidities and complications of CF include CF lung disease, CF liver disease, CF-related diabetes (CFRD), gastrointestinal complications, mental health comorbidities, heart failure, CF-related osteoporosis and osteopenia, and CF-related arthropathy.

SI.6.1 Cystic Fibrosis Lung Disease

Lung disease accounts for the majority of mortality in people with CF. In the US, 62.2% of all 2019 deaths were due to respiratory/cardiorespiratory causes and 16.4% were lung transplant-related.[28]

CF lung disease is also the most prevalent manifestation of CF. The natural history of CF lung disease is one of chronic inflammation and airway infection, and gradual progression driven by intermittent episodes of acute pulmonary exacerbations. This progression typically starts with decreased mucociliary clearance leading to 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 2019, 44.2% of people with CF in the US had at least one positive respiratory culture for *P aeruginosa* as characterised by the Leeds criteria, with 27.7% being characterised as having chronic infection and 16.5% as intermittent infection. The prevalence of having a respiratory culture positive for *S aureus,* methicillin-resistant *S aureus, or Burkholderia cepaciacomplex* was 70.2%, 24.6%, and 2.6%, respectively.[28]

Pulmonary infection is the most clinically impactful complication of CF and the resulting progressive pulmonary dysfunction is the main prognostic factor for people with CF. According to the 2019 report from the CF Registry of Ireland, 34.7% of patients had at least one pulmonary exacerbation requiring intravenous (IV) antibiotics, including 22.4% of children (<18 years) and 43.0% of adults (≥18 years).[29] 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 people with CF, respectively; bronchial wall thickening was identified in 48%, 76%, and 85%, respectively; and mucous plugging was identified in 29%, 51%, and 79%, respectively.[30-32] The prevalence of CT findings in these populations reflects the sampling of relatively older people with CF in these studies.

CF lung disease is characterised by progressive airway obstruction, and its severity is followed serially by measuring 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 had a mean $ppFEV_1$ value of 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.[33] Taken together, these values reflect progressive lung disease from the earliest age at which lung function is measurable.

SI.6.2 Cystic Fibrosis Liver Disease

While there is no standard, universally accepted definition of what constitutes CF liver disease, the majority of people with CF will develop liver abnormalities, including those in liver function tests (LFTs) and changes on ultrasound and/or hepatomegaly, as follows:[34-39]

Liver Abnormalities in Cystic Fibrosis Patients	
Hepatic abnormalities	**Estimated frequency**
Asymptomatic liver function test elevations	10% to >90% (estimates vary widely)
Hepatomegaly	6% to 30% (estimates vary widely)
Steatosis and steatohepatitis	23% to 67%
Neonatal cholestasis	<2%
Focal biliary cirrhosis	11% to 72%
Multilobular cirrhosis	Up to 15%
Portal hypertension	Up to 5%
Synthetic liver failure	Rare
Biliary abnormalities	
Microgallbladder	30%
Cholelithiasis and cholecystitis	Up to 15%
Bile duct stenosis	<2%
Sclerosing cholangitis	<1%
Cholangiocarcinoma	Rare

As defined by a combination of any 2 signs (e.g., hepatomegaly/splenomegaly, increased LFTs, and/or ultrasound liver abnormalities), the cumulative incidence of CF liver disease was 18% in the US, 27% in Italy, and 28% in Israel.[37, 38, 40]

The incidence rate of CF liver disease was 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.[38, 41]

Liver function test abnormalities

Liver abnormalities are very common among CF infants with a cumulative incidence of up to 53% with elevated LFTs by 3 years of age.[42] In 2 large CF patient registries in UK (2021) and Australia (2020), the prevalence of abnormal LFTs in the overall CF population (all ages) was 12.2% and 17.7%, respectively.[13, 43]

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 2.0 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.[44]

If followed for 5 to 10 years, about 35% to 50% of people with CF would have LFT elevations on at least 1 occasion[38, 41] with up to 93% of people with CF with LFT abnormalities over 20 years of follow-up.[45]

Clinically significant liver disease

While LFT or ultrasound liver abnormalities are commonly observed in people with CF, 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 people with CF develop cirrhosis and most of these patients have signs of portal hypertension.[38, 42, 46] In the US patient registry in 2022, prevalence of cirrhosis was 3.0%.[6] In the UK patient registry in 2021, prevalence of cirrhosis

without portal hypertension was 0.9% and prevalence of cirrhosis with portal hypertension was 1.4%.

Despite it being less common than CF lung disease, CF liver disease, including liver failure, remains an important cause of death, accounting for 4.3% of overall CF mortality in the US in 2022[6] and 3.2% of CF mortality in the UK in 2019-2021.[13]

During a 7-year follow-up of 36 children with CF liver disease, 3 (8%) children died from liver failure and 1 (3%) child received a liver transplant. Another 3 (8%) children with CF liver disease died from pulmonary failure. Overall, the mortality at 7 years was 19.4% in the cohort of children with CF liver disease.[47]

SI.6.3 Cystic Fibrosis-Related Diabetes

Three analyses from the Netherlands and US estimated the prevalence of CFRD at approximately 30%.[48-50] The prevalence increased with age, reaching 31%-50% in people with CF 18 years or older.[48-50]

Similarly, in the 2 largest CF patient registries (US and UK), the prevalence of CFRD was 19.0% (overall) in the US and 29.8% (age ≥10 years old) in the UK.[6, 13] CFRD also increased with age, with a prevalence of 4.5% among those <18 years old vs. 29.7% among those ≥18 years old in the US, and 8.3% among those 10-15 years old vs. 35.2% among those ≥16 year old in the UK.[6, 13]

The annual incidence of CFRD was 3.8% in a Danish cohort[51], 3.5% in a British cohort[52], and 2.7% in a US cohort[49]. In the Danish study, the annual incidence increased with age and was 5.0% for patients ≥10 years old and 9.3% for patients ≥20 years old.[53]

Among people with CF, the presence of CFRD has been associated with a more rapid decline in pulmonary function and nutritional status, and with higher mortality, although it is unclear if these associations are causal or due to confounding[53]. Data from the UK CF Registry showed the age-adjusted mortality rate among people with CF with CFRD was 4.2 (95% CI: 3.4 to 5.1) per 100 PY, while the rate in people with CF without CFRD was only 1.5 (95% CI: 1.3 to 1.7) per 100 PY.[54] In a US study, the overall mortality rate for people with CF with CFRD was 1.8 per 100 PY, compared with 0.5 in people with CF without diabetes.[55]

SI.6.4 Cystic Fibrosis-Related Osteoporosis and Osteopenia

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.[56] In 2022, 7.8% and 18.5% of people with CF aged ≥18 years in the US were reported to have osteoporosis and osteopenia, respectively.[6] In the UK in 2021, 6.4% and 14.6% of people with CF aged ≥16 years had osteoporosis and osteopenia, respectively.[56]

Fractures are very common in people with CF, and often more than 1 fracture occurs during the life of a person with CF.[57] Studies estimated that fracture rate was increased twofold in women aged 16 to 34 years and in men aged 25 to 45 years with CF compared to the general population.[58]

Even when people with CF are treated with large supplements of vitamin D and calcium, on average, their bone mineral density remains low.[57-61]

SI.6.5 Cystic Fibrosis-Related Arthropathy

CF-related arthropathy is also a frequent complication in adults with CF. In a cohort study of people with CF in the German CF registry, the prevalence of arthritis/arthropathy was 8.4%

in those ≥18 years of age.[62] In the US CF registry, the prevalence of arthritis/arthropathy was 5.8% among those ≥18 years of age.[6] In the UK CF registry, the prevalence of arthropathy was 3.5% among those ≥16 years old.[13] CF-related arthropathy has been associated with increasing age, female gender, chronic *P. aeruginosa* colonization, and other indicators for disease severity.[62, 63]

SI.6.6 Gastrointestinal Complications

People with CF may have a range of gastrointestinal complications, the onset of which often precedes pulmonary manifestations. Meconium ileus is the earliest gastrointestinal manifestation of CF and occurs in 13-17% of all people with CF at birth.[34, 64]

Gastrointestinal reflux disease is a common complication in people with CF, with an estimated prevalence of 55-90% in adults.[65]

Distal intestinal obstruction syndrome (DIOS) also occurs frequently in people with CF. In a prospective study performed in 9 European countries and Israel between 2009 and 2012, the estimated incidence of DIOS was approximately 8 episodes per 1,000 PY.[66] The risk for DIOS increases after organ transplantation, especially lung transplantation, with an estimated incidence of up to 10-20%.[67] An important differential diagnosis of DIOS is constipation, which is a common complication in both children (lifetime prevalence 26-47%) and adults (lifetime prevalence 42%) with CF.[64]

The cumulative incidence of pancreatic insufficiency, predisposing to fat malabsorption, fat-soluble vitamin (A, D, E, and K) deficiency, steatorrhoea, and failure to thrive, is nearly 90% among people with CF. Among cohorts of people with CF in Canada and the US, 87% had pancreatic insufficiency.[68, 69] In a cohort of patients with CF over 40 years old in the UK, 82% had pancreatic insufficiency, identified via clinical notes.[70] For patients diagnosed with CF on the basis of symptoms, as opposed to asymptomatic screening, pancreatic insufficiency is present in the majority. People diagnosed with CF through newborn screening may not have symptomatic pancreatic insufficiency at the time of CF diagnosis; however, a significant proportion are pancreatic insufficient at birth. Early treatment with pancreatic enzymes and close attention to nutritional management result in improved growth.[71]

SI.6.7 Mental Health Comorbidities

The high burden of mental health complications in people with CF, including depression, anxiety, suicidal ideation, insomnia, and other conditions, is well acknowledged in the published literature and has been documented over the last several decades. This situation may be due to both the indirect psychological impact of living with a chronic debilitating disease as well as direct physiological effects of CF.

Depression and anxiety are the best documented mental health complications affecting people with CF. The reported prevalence of these diagnoses in people with CF varies depending on the population and diagnostic criteria used and may be as high as 30% (2 to 3 times higher than the general population). For instance, in the International Depression Epidemiological Study conducted by Quittner et al. including data from 6,088 people with CF across 9 countries, 5 to 19% of adolescents and 13 to 29% of adults had elevated symptoms of depression; 22% of adolescents and 32% of adults had symptoms of anxiety.[72]

Suicidal ideation is also more common in people with CF than in the general population, with a prevalence of up to 11% in adults and up to 22% in adolescents (compared to approximately 5% in adults and 13% in adolescents in the general population).[73-75]

In addition to increased risk of depression, anxiety, and suicidal ideation, people with CF have also been reported to have poorer sleep quality as compared to the general population.

Studies report disturbed sleep in more than 50% of CF patients, especially those with advanced lung disease or patients on the lung transplant waiting list.[76-78] Further, people with CF may be disproportionately affected by other mental health conditions such as attention-deficit/hyperactivity disorder (ADHD)[79, 80]; these mental health diagnoses can manifest through a variety of symptoms (including aggression, agitation, memory issues, and confusion).

In addition to a documented higher burden of mental health conditions in the CF population compared to the general population, the incidence and prevalence of these conditions in people with CF continue to increase over time, mirroring general population trends. For instance, the US National Survey on Drug Use and Health (NDUH) demonstrated that prevalence of depression (major depression episode in the past 12 months) in US adults increased from 6.9% in 2012 to 7.8% in 2019.[81] During the same time period, prevalence of depression in adult people with CF in the US increased from 22.2% in 2012 to 28.3% in 2019.[82, 83]

Furthermore, substantial increases in mental health conditions were reported in the general population following the onset of the COVID-19 pandemic. In 1 survey comparing US adults in June 2020 (peak of pandemic lock-down) to the similar time of the year in 2019 (prepandemic), the prevalence of anxiety disorders was 3 times higher (25.5% vs. 8.1%), depressive disorders was 4 times higher (24.3% vs. 6.5%), and prevalence of suicidal ideation was 2 times higher (10.7% vs. 4.3%).[84]

SI.6.5 Heart Failure

Progressive hypoxia due to severe lung disease can result in CF-related cardiac disease, which can manifest as right ventricular dysfunction and cor pulmonale. The prevalence of cor pulmonale varies from 6% to 70% based on postmortem studies.[85, 86]

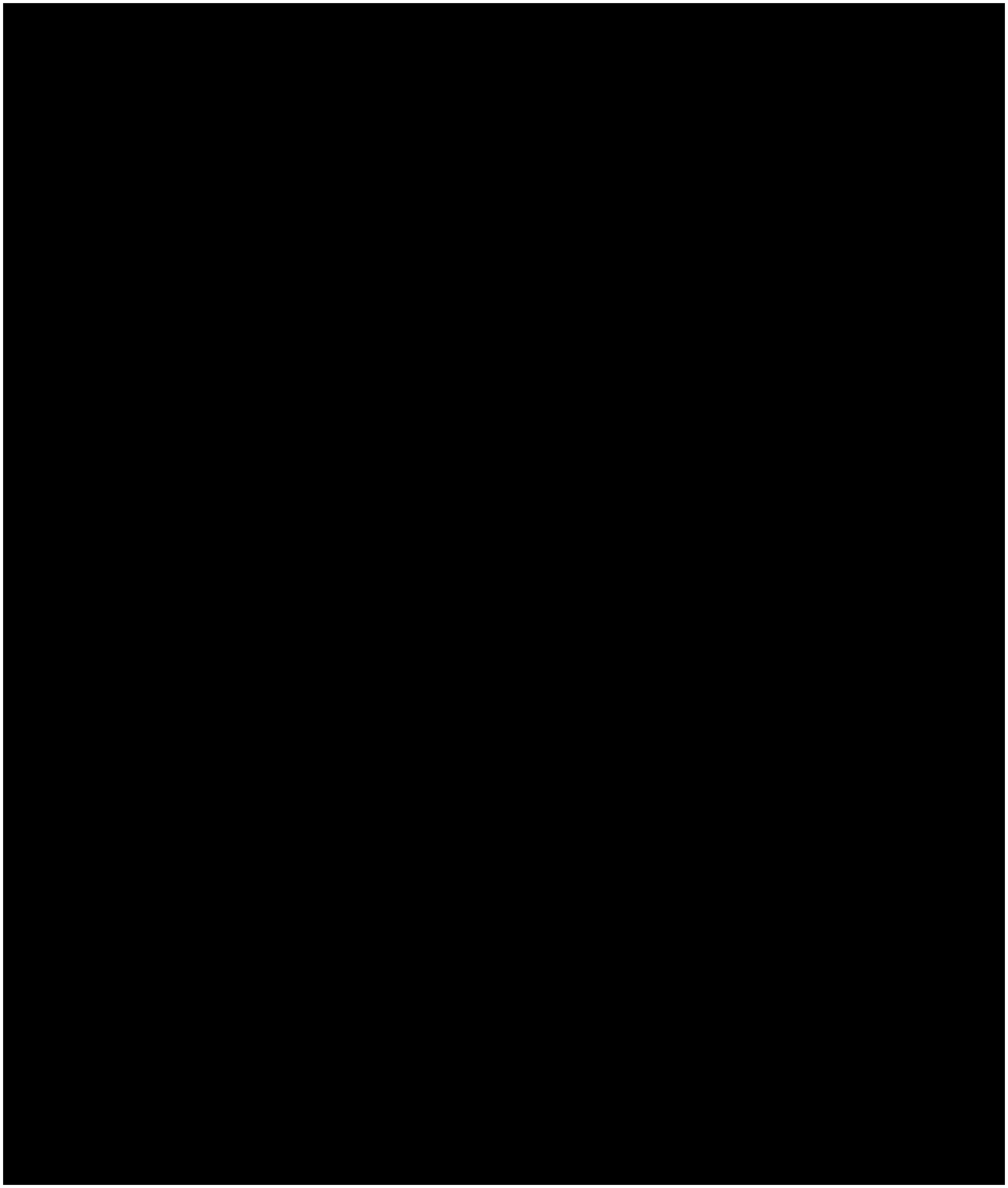
In a cohort of people with CF in Ohio, US, general heart failure was detected in 8.3%.[87] Among the 61 people with CF and heart failure, the mean and median survival was 8 months and 4 months, respectively.[87] Of 170 people with CF who died, 55 (32%) had overt right heart failure at least 2 weeks before death.

There are no estimates of the incidence or prevalence of ischemic heart disease among people with CF because, historically, it has not been reported. However, given the high-fat diet and prevalence of CFRD, there is speculation that as more people 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.[88]

SII Nonclinical Part of the Safety Specification

Nonclinical studies were conducted to evaluate the pharmacologic activity of VNZ and D-IVA, and to characterise their pharmacokinetic (PK) and toxicity profiles (Module 2.4). D-IVA is a deuterated isotopolog of IVA that was designed to improve its metabolic stability and PK. TEZ and IVA were previously evaluated in similar sets of studies to support the clinical development of Symdeko/Symkevi and Kalydeco, respectively. A 13-week combination toxicity study of VNZ, TEZ and D-IVA in rats was conducted to evaluate potential additive or synergistic effects when VNZ was administered in dual (VNZ/D-IVA) or triple combination (TC).

[redacted]



SII.2 Safety Pharmacology

Results from safety pharmacology studies and secondary pharmacodynamic screening evaluating VNZ, TEZ, and D-IVA/IVA suggest a high degree of selectivity and a low potential for adverse biological or physiological effects when VNZ, TEZ, and D-IVA are administered in combination. Furthermore, in a thorough QTc study, there were no clinically important trends attributable to VNZ dosing identified in vital sign assessments, heart rate, and no effects were noted in ECG data, including QTc prolongation.

SII.3 Pharmacokinetics

Nonclinical ADME and PK properties of VNZ, D-IVA and TEZ have been adequately characterised to support registration of VNZ/TEZ/D-IVA.

VNZ, TEZ, and D-IVA were orally bioavailable in all species tested. Systemic exposures to VNZ, TEZ, and D-IVA in combination studies in rats were similar (<2-fold) to the exposures observed when these compounds were dosed individually. Adequate exposures of VNZ, TEZ, and D-IVA were achieved for nonclinical safety evaluation.

After oral administration of ^{14}C-VNZ, ^{14}C-TEZ, and ^{14}C-D-IVA, radioactivity was rapidly distributed across most tissues in rats, with no selective binding to melanin containing tissues. Placental transfer of ^{14}C-VNZ and ^{14}C-TEZ was observed in pregnant rats. Based on available data with ^{14}C-IVA, D-IVA is expected to cross the placenta in pregnant rats. Protein binding is high for VNZ, TEZ, and D-IVA in plasma of all species tested and is similar across species.

VNZ and D-IVA are eliminated primarily via oxidative metabolism, whereas TEZ also undergoes glucuronidation in addition to oxidation. VNZ metabolism was similar between nonclinical species and humans. There are no major circulating metabolites of VNZ in humans. The overall in vitro and in vivo ADME properties of D-IVA, including its metabolic pathways, are qualitatively similar to those for IVA. Thus, ADME and preclinical safety data for IVA were leveraged, where needed. Metabolism of TEZ has been fully characterised previously in support of registration of Symdeko/Symkevi. Based on the totality of the available data, all major metabolites of TEZ and D-IVA are considered adequately qualified in nonclinical toxicity studies.

CYP and transporter DDI risks of VNZ, TEZ, D-IVA and their major human metabolites were fully evaluated in vitro per FDA Guidance and the results were used to inform follow-up clinical evaluation. Both transporter- and CYP-mediated DDI risks of VNZ, TEZ, D-IVA and their metabolites as perpetrator are predicted to be low at clinically relevant exposures. VNZ, TEZ, and D-IVA are substrates of CYP3A, and thus, concomitant use of CYP3A inducers or inhibitors may affect their exposures.

SII.4 Other Toxicity-Related Information or Data

Results of the photosafety assessment indicate that there is a very low probability of phototoxicity associated with VNZ and TEZ administration in humans. Phototoxicity testing was not conducted with IVA due to a lack of significant partitioning or binding to melanin containing tissues (skin or eye).

SIII Clinical Trial Exposure

Cumulatively, an estimated 1,306 subjects have been exposed to at least 1 dose of VNZ (as either monotherapy or combination therapy) in clinical studies: 1,041 were subjects with CF and 265 were healthy subjects. By comparison, in the VNZ development programme, a total of 63 subjects have been exposed to at least 1 dose of placebo (12 were CF subjects and 51 were healthy subjects), and a total of 500 subjects (all CF subjects) have been exposed to an active comparator (e.g., TEZ/IVA, ELX/TEZ/IVA) (Table 1.

Exposure in the VNZ development clinical studies was calculated using patient years (PY). As shown in Table 2, subjects were exposed to VNZ treatment during clinical studies for approximately 1083.84 PY, in comparison to 3.17 PY for the placebo subjects, and 511.79 PY for the active comparator subjects.

The cumulative subject exposure by age, sex, race, and region are provided in Table 3, Table 4, Table 5, and Table 6, respectively. Overall, of the 1,306 subjects exposed to VNZ treatment, [redacted] were aged ≥18 years [redacted], [redacted], and from North America [redacted]. There were more [redacted] than [redacted] on VNZ treatment.

Table 1 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Dose

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Dose	**N = 315**	**Total Exposure (PY)**	**N = 1135**	**Total Exposure (PY)**	**N = 1450**	**Total Exposure (PY)**
Total	315	8.68	1135	1590.48	1450	1599.15
Active (combination and monotherapy)	265	6.15	1041	1077.68	1306	1083.84
Combination (VNZ TC)	152	2.82	1041	1077.68	1193	1080.51
VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd	51	0.29	914	1013.68	965	1013.98
Other VNZ combination	119	2.53	147	64.00	266	66.53
Monotherapy (VNZ)	131	3.33	0	--	131	3.33
VNZ <20 mg	89	1.96	0	--	89	1.96
VNZ ≥20 mg	68	1.38	0	--	68	1.38
Placebo	51	2.17	12	1.00	63	3.17
Active Comparator in VNZ Studies	0	--	500	511.79	500	511.79
ELX/TEZ/IVA	0	--	491	510.93	491	510.93
TEZ/IVA	0	--	10	0.86	10	0.86

CF: cystic fibrosis; CSR: clinical study report; D-IVA: deutivacator, also known as VX-561; ELX: elexacaftor, also known as VX-445; ELX/TEZ/IVA: ELX in combination with TEZ and IVA, also known as or Trikafta™ or Kaftrio™; IVA: ivacaftor; also known as VX-770 or Kalydeco™; N: number of subjects in the Safety Set; PY: patient year (1 year = 48 weeks); qd: daily; TC: triple combination; TEZ: tezacaftor, also known as VX-661; TEZ/IVA: TEZ in combination with IVA, also known as Symdeko™ or Symkevi ™; TFL: tables, figures, listings; VNZ: vanzacaftor, also known as VX-121

Notes: Safety Set includes all subjects who received any amount of vanzacaftor alone (monotherapy), vanzacaftor in combination with tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) or ivacaftor (VNZ/TEZ/IVA), or placebo, or active comparator (ELX/TEZ/IVA or TEZ/IVA) and had the dosing information included in the clinical database by 12 February 2024. A subject may be counted in multiple rows but only once in each row.

a Includes the following completed studies in healthy subjects with the final CSR TFLs available: 121-001 (Part A, B, C), 121-003, 121-004, 121-005, 121-006, 121-007, 121-008, 121-009, and 121-013.

b Includes the following completed studies in CF subjects with the final CSR TFLs available: 121-001 (Part D), 121-101, 121-102, 121-103, and 121-105 (Part A1, B1); and the following ongoing studies in CF subjects: 121-104 and 121-106.

Table 2 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Duration

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Duration	**N = 315**	**Total Exposure (PY)**	**N = 1135**	**Total Exposure (PY)**	**N = 1450**	**Total Exposure (PY)**
Total	315	8.68	1135	1590.48	1450	1599.15
1 day	63	0.19	2	0.01	65	0.19
>1 day to ≤4 weeks	252	8.49	32	2.17	284	10.66
>4 weeks to ≤24 weeks	0	--	95	15.02	95	15.02
>24 to ≤52 weeks	0	--	157	144.07	157	144.07
≤52 weeks	315	8.68	286	161.26	601	169.93
>52 weeks	0	--	849	1429.22	849	1429.22

Table 2 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Duration

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Duration	**N = 315**	**Total Exposure (PY)**	**N = 1135**	**Total Exposure (PY)**	**N = 1450**	**Total Exposure (PY)**
Active (combination and monotherapy)	265	6.15	1041	1077.68	1306	1083.84
1 day	57	0.17	0	--	57	0.17
>1 day to ≤4 weeks	208	5.98	25	1.71	233	7.69
>4 weeks to ≤24 weeks	0	--	235	67.39	235	67.39
>24 to ≤52 weeks	0	--	341	281.13	341	281.13
≤52 weeks	265	6.15	601	350.22	866	356.37
>52 weeks	0	--	440	727.47	440	727.47
Combination (VNZ TC)	152	2.82	1041	1077.68	1193	1080.51
1 day	27	0.08	0	--	27	0.08
>1 day to ≤4 weeks	125	2.74	25	1.71	150	4.45
>4 weeks to ≤24 weeks	0	--	235	67.39	235	67.39
>24 to ≤52 weeks	0	--	341	281.13	341	281.13
≤52 weeks	152	2.82	601	350.22	753	353.04
>52 weeks	0	--	440	727.47	440	727.47
Monotherapy (VNZ)	131	3.33	0	--	131	3.33
1 day	30	0.09	0	--	30	0.09
>1 day to ≤4 weeks	101	3.24	0	--	101	3.24
>4 weeks to ≤24 weeks	0	--	0	--	0	--
>24 to ≤52 weeks	0	--	0	--	0	--
≤52 weeks	131	3.33	0	--	131	3.33
>52 weeks	0	--	0	--	0	--
Placebo	51	2.17	12	1.00	63	3.17
1 day	8	0.02	1	0.00	9	0.03
>1 day to ≤4 weeks	43	2.14	4	0.33	47	2.47
>4 weeks to ≤24 weeks	0	--	7	0.67	7	0.67
>24 to ≤52 weeks	0	--	0	--	0	--
≤52 weeks	51	2.17	12	1.00	63	3.17
>52 weeks	0	--	0	--	0	--
Active Comparator in VNZ Studies	0	--	500	511.79	500	511.79
1 day	0	--	1	0.00	1	0.00
>1 day to ≤4 weeks	0	--	6	0.27	6	0.27
>4 weeks to ≤24 weeks	0	--	20	3.85	20	3.85
>24 to ≤52 weeks	0	--	322	342.53	322	342.53
≤52 weeks	0	--	349	346.66	349	346.66
>52 weeks	0	--	151	165.13	151	165.13

CF: cystic fibrosis; CSR: clinical study report; N: number of subjects in the Safety Set; PY: patient year (1 year = 48 weeks); qd: daily; TC: triple combination; TFL: tables, figures, listings; VNZ: vanzacaftor, also known as VX-121

Notes: Safety Set includes all subjects who received any amount of vanzacaftor alone (monotherapy), vanzacaftor in combination with tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) or ivacaftor (VNZ/TEZ/IVA), or placebo, or active comparator (ELX/TEZ/IVA or TEZ/IVA) and had the dosing information included in the clinical database by 12 February 2024. A subject may be counted in multiple rows but only once in each row.

A Includes the following completed studies in healthy subjects with the final CSR TFLs available: 121-001 (Part A, B, C), 121-003, 121-004, 121-005, 121-006, 121-007, 121-008, 121-009, and 121-013.

B Includes the following completed studies in CF subjects with the final CSR TFLs available: 121-001 (Part D), 121-101, 121-102, 121-103, and 121-105 (Part A1, B1); and the following ongoing studies in CF subjects: 121-104 and 121-106.

Table 3 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Age

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Age (Years)	N = 315	Total Exposure (PY)	N = 1135	Total Exposure (PY)	N = 1450	Total Exposure (PY)
Total	315	8.68	1135	1590.48	1450	1599.15
≥6 to <12 years	0	--	81	67.39	81	67.39
≥12 to <18 years	0	--	136	203.59	136	203.59
≥18 to <65 years	306	8.65	915	1313.54	1221	1322.18
≥65 years	9	0.03	3	5.96	12	5.99
≥18 years	315	8.68	918	1319.50	1233	1328.17
Active (combination and monotherapy)	265	6.15	1041	1077.68	1306	1083.84
≥6 to <12 years	0	--	81	67.39	81	67.39
≥12 to <18 years	0	--	122	134.75	122	134.75
≥18 to <65 years	256	6.13	835	870.67	1091	876.80
≥65 years	9	0.03	3	4.88	12	4.90
≥18 years	265	6.15	838	875.55	1103	881.70
Combination (VNZ TC)	152	2.82	1041	1077.68	1193	1080.51
≥6 to <12 years	0	--	81	67.39	81	67.39
≥12 to <18 years	0	--	122	134.75	122	134.75
≥18 to <65 years	143	2.79	835	870.67	978	873.47
≥65 years	9	0.03	3	4.88	12	4.90
≥18 years	152	2.82	838	875.55	990	878.37
Monotherapy (VNZ)	131	3.33	0	--	131	3.33
≥6 to <12 years	0	--	0	--	0	--
≥12 to <18 years	0	--	0	--	0	--
≥18 to <65 years	131	3.33	0	--	131	3.33
≥65 years	0	--	0	--	0	--
≥18 years	131	3.33	0	--	131	3.33
Placebo	51	2.17	12	1.00	63	3.17
≥6 to <12 years	0	--	0	--	0	--
≥12 to <18 years	0	--	0	--	0	--
≥18 to <65 years	51	2.17	12	1.00	63	3.17
≥65 years	0	--	0	--	0	--
≥18 years	51	2.17	12	1.00	63	3.17
Active Comparator in VNZ Studies	0	--	500	511.79	500	511.79
≥6 to <12 years	0	--	0	--	0	--
≥12 to <18 years	0	--	69	68.85	69	68.85
≥18 to <65 years	0	--	430	441.86	430	441.86
≥65 years	0	--	1	1.08	1	1.08
≥18 years	0	--	431	442.94	431	442.94

CF: cystic fibrosis; CSR: clinical study report; N: number of subjects in the Safety Set; PY: patient year (1 year = 48 weeks); qd: daily; TC: triple combination; TFL: tables, figures, listings; VNZ: vanzacaftor, also known as VX-121

Notes: Safety Set includes all subjects who received any amount of vanzacaftor alone (monotherapy), vanzacaftor in combination with tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) or ivacaftor (VNZ/TEZ/IVA), or placebo, or active comparator (ELX/TEZ/IVA or TEZ/IVA) and had the dosing information included in the clinical database by 12 February 2024. A subject may be counted in multiple rows but only once in each row.

A Includes the following completed studies in healthy subjects with the final CSR TFLs available: 121-001 (Part A, B, C), 121-003, 121-004, 121-005, 121-006, 121-007, 121-008, 121-009, and 121-013.

B Includes the following completed studies in CF subjects with the final CSR TFLs available: 121-001 (Part D), 121-101, 121-102, 121-103, and 121-105 (Part A1, B1); and the following ongoing studies in CF subjects: 121-104 and 121-106.

Table 4 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Sex

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Sex	N = 315	Total Exposure (PY)	N = 1135	Total Exposure (PY)	N = 1450	Total Exposure (PY)
Total	315	8.68	1135	1590.48	1450	1599.15
[redacted]						
Active (combination and monotherapy)	265	6.15	1041	1077.68	1306	1083.84
[redacted]						
Combination (VNZ TC)	152	2.82	1041	1077.68	1193	1080.51
[redacted]						
Monotherapy (VNZ)	131	3.33	0	--	131	3.33
[redacted]						
Placebo	51	2.17	12	1.00	63	3.17
[redacted]						
Active Comparator in VNZ Studies	0	--	500	511.79	500	511.79
[redacted]						

CF: cystic fibrosis; CSR: clinical study report; N: number of subjects in the Safety Set; PY: patient year (1 year = 48 weeks); qd: daily; TC: triple combination; TFL: tables, figures, listings; VNZ: vanzacaftor, also known as VX-121

Notes: Safety Set includes all subjects who received any amount of vanzacaftor alone (monotherapy), vanzacaftor in combination with tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) or ivacaftor (VNZ/TEZ/IVA), or placebo, or active comparator (ELX/TEZ/IVA or TEZ/IVA) and had the dosing information included in the clinical database by 12 February 2024. A subject may be counted in multiple rows but only once in each row.

A Includes the following completed studies in healthy subjects with the final CSR TFLs available: 121-001 (Part A, B, C), 121-003, 121-004, 121-005, 121-006, 121-007, 121-008, 121-009, and 121-013.

B Includes the following completed studies in CF subjects with the final CSR TFLs available: 121-001 (Part D), 121-101, 121-102, 121-103, and 121-105 (Part A1, B1); and the following ongoing studies in CF subjects: 121-104 and 121-106.

Table 5 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Race

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Race	N = 315	Total Exposure (PY)	N = 1135	Total Exposure (PY)	N = 1450	Total Exposure (PY)
Total	315	8.68	1135	1590.48	1450	1599.15
[redacted]						

Table 5 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Race

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Race	**N = 315**	**Total Exposure (PY)**	**N = 1135**	**Total Exposure (PY)**	**N = 1450**	**Total Exposure (PY)**
[redacted]						
Active (combination and monotherapy)	265	6.15	1041	1077.68	1306	1083.84
[redacted]						
Combination (VNZ TC)	152	2.82	1041	1077.68	1193	1080.51
[redacted]						
Monotherapy (VNZ)	131	3.33	0	--	131	3.33
[redacted]						
Placebo	51	2.17	12	1.00	63	3.17
[redacted]						

Table 5 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Race

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Race	N = 315	Total Exposure (PY)	N = 1135	Total Exposure (PY)	N = 1450	Total Exposure (PY)
Active Comparator in VNZ Studies	0	--	500	511.79	500	511.79
[redacted]						

CF: cystic fibrosis; CSR: clinical study report; N: number of subjects in the Safety Set; PY: patient year (1 year = 48 weeks); qd: daily; TC: triple combination; TFL: tables, figures, listings; VNZ: vanzacaftor, also known as VX-121

Notes: Safety Set includes all subjects who received any amount of vanzacaftor alone (monotherapy), vanzacaftor in combination with tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) or ivacaftor (VNZ/TEZ/IVA), or placebo, or active comparator (ELX/TEZ/IVA or TEZ/IVA) and had the dosing information included in the clinical database by 12 February 2024. A subject may be counted in multiple rows but only once in each row.

A Includes the following completed studies in healthy subjects with the final CSR TFLs available: 121-001 (Part A, B, C), 121-003, 121-004, 121-005, 121-006, 121-007, 121-008, 121-009, and 121-013.

B Includes the following completed studies in CF subjects with the final CSR TFLs available: 121-001 (Part D), 121-101, 121-102, 121-103, and 121-105 (Part A1, B1); and the following ongoing studies in CF subjects: 121-104 and 121-106.

Table 6 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Region

	Healthy Subjects[a]		Subjects With CF[b]		Overall	
Race	N = 315	Total Exposure (PY)	N = 1135	Total Exposure (PY)	N = 1450	Total Exposure (PY)
Total	315	8.68	1135	1590.48	1450	1599.15
[redacted]						
Active (combination and monotherapy)	265	6.15	1041	1077.68	1306	1083.84
[redacted]						
Combination (VNZ TC)	152	2.82	1041	1077.68	1193	1080.51
[redacted]						
Monotherapy (VNZ)	131	3.33	0	--	131	3.33
[redacted]						
Placebo	51	2.17	12	1.00	63	3.17

Table 6 Summary of Exposure in the Vanzacaftor Clinical Development Programme by Region

Race	Healthy Subjects[a] N = 315	Healthy Subjects[a] Total Exposure (PY)	Subjects With CF[b] N = 1135	Subjects With CF[b] Total Exposure (PY)	Overall N = 1450	Overall Total Exposure (PY)
[redacted]						
Active Comparator in VNZ Studies	**0**	**--**	**500**	**511.79**	**500**	**511.79**
[redacted]						

CF: cystic fibrosis; CSR: clinical study report; N: number of subjects in the Safety Set; PY: patient year (1 year = 48 weeks); qd: daily; TC: triple combination; TFL: tables, figures, listings; VNZ: vanzacaftor, also known as VX-121

Notes: Safety Set includes all subjects who received any amount of vanzacaftor alone (monotherapy), vanzacaftor in combination with tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) or ivacaftor (VNZ/TEZ/IVA), or placebo, or active comparator (ELX/TEZ/IVA or TEZ/IVA) and had the dosing information included in the clinical database by 12 February 2024. A subject may be counted in multiple rows but only once in each row.

A Includes the following completed studies in healthy subjects with the final CSR TFLs available: 121-001 (Part A, B, C), 121-003, 121-004, 121-005, 121-006, 121-007, 121-008, 121-009, and 121-013.

B Includes the following completed studies in CF subjects with the final CSR TFLs available: 121-001 (Part D), 121-101, 121-102, 121-103, and 121-105 (Part A1, B1); and the following ongoing studies in CF subjects: 121-104, 121-106.

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	VNZ/TEZ/D-IVA did not show unfavourable effects on these conditions during study. VNZ/TEZ/D-IVA improves overall pulmonary condition ($ppFEV_1$ and rate of pulmonary exacerbations, particularly those requiring IV antibiotic treatment and hospitalisation) in patients with CF.
Pregnancy, planning of pregnancy, or lactation	
Reason for exclusion	As a standard precautionary measure, pregnant and lactating women were excluded from clinical studies.
Is it to be considered missing information?	Yes
Rationale	Not applicable
Significant liver disease	

Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme	
Reason for exclusion	As a precautionary measure, subjects with significant liver disease at screening were excluded from clinical studies.
Is it to be considered missing information?	Yes
Rationale	Hepatoxicity during treatment with VNZ/TEZ/D-IVA is addressed as an important potential 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 VNZ, TEZ, and D-IVA elimination, and renal clearance is not expected to play a significant role in the elimination of VNZ/TEZ/D-IVA.
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	VNZ, TEZ, and D-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 VNZ/TEZ/D-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	VNZ/TEZ/D-IVA improves overall pulmonary condition in CF patients. VNZ/TEZ/D-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	
Reason for exclusion	VNZ, TEZ, and D-IVA are CYP3A substrates and co-administration with inhibitors or inducers of CYP3A may modify the exposure of VNZ/TEZ/D-IVA and alter study results.
Is it to be considered missing information?	No
Rationale	The potential interactions between VNZ/TEZ/D-IVA and CYP3A inducers or inhibitors.

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator protein; CYP3A: cytochrome P450 subfamily 3A; D-IVA: deutivacaftor; ppFEV$_1$: forced expiratory volume in 1 second; TEZ: tezacaftor; VNZ: vanzacaftor; VNZ/TEZ/D-IVA: VNZ in combination with TEZ and D-IVA

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.

Type of Special Population	Exposure
Patients with hepatic impairment	A dedicated study (Study VX21-121-008 [Study 008]) evaluating the safety and PK of a single dose of VNZ/TEZ/D-IVA in 12 subjects without CF who have moderate hepatic impairment has been conducted. A single dose of VNZ/TEZ/D-IVA was generally safe and well tolerated in subjects without CF who have moderate hepatic impairment and matched healthy volunteers. No studies in patients with severe hepatic impairment are planned. In the controlled, Phase 3 studies (Studies VX20-121-102 [Study 102] and VX20-121-103 [Study 103]) in CF subjects 12 years of age and older, 8 subjects with an ongoing medical history of portal hypertension, hepatic cirrhosis, and/or portal/hepatic fibrosis received VNZ/TEZ/D-IVA treatment. The safety data in these 8 subjects were generally consistent with the safety data in other subjects treated with VNZ/TEZ/D-IVA. 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) in CF subjects 12 years of age and older, 1 subject with a medical history of chronic kidney disease received VNZ/TEZ/D-IVA treatment. Renal excretion is not a major pathway of VNZ, TEZ, and D-IVA elimination, and renal clearance is not expected to play a significant role in the elimination of VNZ/TEZ/D-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) in CF subjects 12 years of age and older, 11 subjects with non-missing $ppFEV_1$ <40 at baseline received VNZ/TEZ/D-IVA treatment. In the open-label, Phase 3 study (Study VX21-121-105 [Study 105]) in CF subjects 6 through 11 years of age, 1 subject with non-missing $ppFEV_1$ <40 at baseline received VNZ/TEZ/D-IVA treatment. Overall, the safety data in these 12 subjects were consistent with the safety data in other subjects treated with VNZ/TEZ/D-IVA.
Population with relevant different racial or 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.

CF: cystic fibrosis; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; Study 008: VX21-121-008; Study 102: VX20-121-102; Study 103: VX20-121-103; Study 105: VX21-121-105; VNZ/TEZ/D-IVA: vanzacaftor in combination with tezacaftor and deutivacaftor

SV Post-authorisation Experience

Not applicable

SVI Additional EU Requirements for Safety Specification

Potential for Misuse for Illegal Purposes

No systematic examination of the abuse potential of VNZ, TEZ, or D-IVA was performed in the VNZ 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, VNZ/TEZ/D-IVA use is not expected to have the potential for misuse for illegal purposes.

VNZ/TEZ/D-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 adverse drug reactions (ADRs) are described in Section 4.8 (Undesirable Effects) of the EU Summary of Product Characteristics (SmPC) but are not considered to be important risks for VNZ/TEZ/D-IVA given the events in clinical studies were mostly mild to moderate in severity and non-serious, with few study drug discontinuations.

Overall, the ADRs are not expected to have a significant impact on the VNZ/TEZ/D-IVA benefit-risk profile and will be followed up via routine pharmacovigilance, including signal detection activities and adverse reaction reporting.

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

Descriptions of the initially proposed important identified risks, important potential risks, and missing information for VNZ/TEZ/D-IVA are provided herein; changes will be captured in Section SVII.2.

SVII.1.2.1 Important Identified Risk – Hepatotoxicity

Benefit-Risk Impact
In the two 52 week, double-blinded, controlled Phase 3 pivotal studies (Studies 102 and 103) in CF subjects 12 years of age and older and the open-label, Phase 3 study (Study 105) in CF subjects 6 through 11 years of age, transaminase elevations have been reported. In some cases, a contributory role of VNZ/TEZ/D-IVA cannot be excluded.

Based on the overall safety experience with VNZ/TEZ/D-IVA, including clinical and nonclinical data, hepatotoxicity is considered an important identified risk.

The important identified risk of hepatotoxicity does not impact the benefit-risk profile of VNZ/TEZ/D-IVA.

SVII.1.2.2 Important Potential Risk – Cataract

Benefit-Risk Impact
Cases of non-congenital lens opacities without impact on vision have been reported in CF subjects less than 18 years of age treated with IVA-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation), a possible risk attributable to treatment with IVA cannot be excluded. As such, cataract is considered a potential risk for IVA-containing regimen. As D-IVA is a deuterated isotopologue of IVA, the potential risk of cataract is considered applicable to D-IVA containing regimen.

The important potential risk of cataract does not impact the benefit-risk profile of VNZ/TEZ/D-IVA.

SVII.1.2.3 Missing Information – Use in Pregnancy or Breastfeeding

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

The effect of VNZ/TEZ/D-IVA on pregnancy and breastfeeding in humans is not known as no clinical studies in pregnancy or breastfeeding have been conducted. Therefore, the safety in this population is considered missing information and further characterisation is needed.

No impact on the benefit-risk profile of VNZ/TEZ/D-IVA is expected.

SVII.1.2.4 Missing Information – Long-term Safety

Benefit-Risk Impact
The longest clinical study exposure to VNZ/TEZ/D-IVA treatment in the pivotal Studies 102 and 103 is approximately 54 weeks.

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

No impact on the benefit-risk profile of VNZ/TEZ/D-IVA is expected.

SVII.1.2.5 Missing Information – Use in Patients With Moderate or Severe Hepatic Impairment

Benefit-Risk Impact
A dedicated study (Study 008) has been conducted to evaluate the safety and PK of VNZ/TEZ/D-IVA in 12 subjects without CF who have moderate hepatic impairment. Based on the final results from this study, a single dose of VNZ/TEZ/D-IVA was generally safe and

well tolerated in subjects without CF who have moderate hepatic impairment and matched healthy volunteers. The PK results for VNZ/TEZ/D-IVA were similar in subjects with moderate hepatic impairment and matched healthy subjects.

In the controlled, Phase 3 studies (Studies 102 and 103) in CF subjects 12 years of age and older, 8 subjects with an ongoing medical history of portal hypertension, hepatic cirrhosis, and/or portal/hepatic fibrosis received VNZ/TEZ/D-IVA treatment. The safety data in these 8 subjects were generally consistent with the safety data in other subjects treated with VNZ/TEZ/D-IVA.

Overall, the safety experience in patients with moderate or severe hepatic impairment is limited; therefore, the use of VNZ/TEZ/D-IVA in this population is considered missing information.

No impact on the benefit-risk profile of VNZ/TEZ/D-IVA is expected.

SVII.1.2.6 Missing Information – Use in Children Aged 6 to 11 Years

Benefit-Risk Impact

CF subjects 6 through 11 years of age were evaluated for up to 24 weeks with VNZ/TEZ/D-IVA period in the Phase 3 Study 105. The safety data from the completed Cohorts A1 and B1 was generally consistent with the safety data in other subjects treated with VNZ/TEZ/D-IVA; however, the study had a relatively small sample size of 95 subjects (17 subjects in Cohort A1 and 78 subjects in Cohort B1), and the overall safety experience is still limited; therefore, use in this age group is considered missing information and further characterisation is needed.

No impact on the benefit-risk profile of VNZ/TEZ/D-IVA is expected.

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

Not applicable.

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 – Hepatotoxicity

Potential mechanisms

VNZ, TEZ, and D-IVA are primarily metabolised by liver enzymes; however, the exact mechanism of the effect of VNZ/TEZ/D-IVA to cause hepatotoxicity is not presently known.

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

Evidence source(s) and strength of evidence
In the two 52 week, double-blinded, controlled Phase 3 pivotal studies (Studies 102 and 103) in CF subjects 12 years of age and older and the open-label, Phase 3 study (Study 105) in CF subjects 6 through 11 years of age, transaminase elevations have been reported. In some cases, a contributory role of VNZ/TEZ/D-IVA cannot be excluded.Based on the overall safety experience with VNZ/TEZ/D-IVA, including clinical and nonclinical data, hepatotoxicity is considered an important identified risk.

Characterisation of the risk

In the two 52 week, double-blinded, controlled Phase 3 pivotal studies (Studies 102 and 103) in CF subjects 12 years of age and older, 43 (9.0%) subjects receiving VNZ/TEZ/D-IVA had at least 1 elevated transaminase event. The majority of these events were mild or moderate in severity. Two (0.4%) subjects had serious elevated transaminase events.

There were 7 (1.5%) subjects that had elevated transaminase events that led to treatment discontinuation, and 5 (1.0%) subjects had elevated transaminase events that led to treatment interruption.

The majority of subjects had ALT/aspartate aminotransferase (AST) values that remained within the normal range. Twenty-nine (6.0%), 12 (2.5%) and 6 (1.3%) subjects had ALT or AST >3 ×, 5 × and 8 × ULN, respectively.

One (0.2%) subject had [redacted] concurrent with a newly occurring [redacted].

In the open-label, Phase 3 study (Study 105) in CF subjects 6 through 11 years of age, the results were generally consistent with those from Studies 102 and 103.

During Study 105 Cohort B1, subjects received VNZ/TEZ/D-IVA for a 24 week treatment period. There were 4 (5.1%) subjects receiving VNZ/TEZ/D-IVA that had at least 1 elevated transaminase event. All the events were mild or moderate in severity and there were no serious elevated transaminase events. There were no elevated transaminase events that led to treatment discontinuation or interruption.

The majority of subjects had ALT/AST values that remained within the normal range. Two (2.6) subjects had ALT or AST >3 × and 1 (1.3%) subject had ALT or AST > 5 × ULN. There were no transaminase elevations > 8× ULN. No subject had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN.

Risk factors and risk groups
Generally known risk factors for hepatotoxicity 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.

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 VNZ/TEZ/D-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.

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

The potential 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. 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. As D-IVA is a deuterated isotopologue of IVA, a possible risk attributable to treatment with D-IVA cannot be excluded.

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 12 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. As D-IVA is a deuterated isotopologue of IVA, the potential risk of cataract is considered applicable to D-IVA containing regimen.

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.

Risk factors and risk groups
Risk factors for cataracts include aging, trauma, UV light and radiation exposure, diabetes mellitus, intraocular inflammation, and corticosteroid use.[89-92]

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 VNZ/TEZ/D-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 Pregnancy or Breastfeeding

Evidence source
Nonclinical studies indicated that VNZ, TEZ, and D-IVA are not teratogens. Additional nonclinical studies showed VNZ/TEZ and IVA were transferred to the placenta of pregnant rats and execrated into the milk of lactating rats.

The effect of VNZ/TEZ/D-IVA on pregnancy and breastfeeding in humans is not known as no clinical studies in pregnancy or breastfeeding have been conducted.

Population in need of further characterisation
The safety of VNZ/TEZ/D-IVA treatment in pregnancy will be further characterised in the postauthorisation setting.

SVII.3.3.2 Missing Information – Long-term Safety

Evidence source
The longest clinical study exposure to VNZ/TEZ/D-IVA treatment in the pivotal Studies 102 and 103 is approximately 54 weeks.

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

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

Evidence source

A dedicated study (Study 008) has been conducted to evaluate the safety and PK of a single dose of VNZ/TEZ/D-IVA in 12 subjects without CF who have moderate hepatic impairment. Based on the final results from this study, a single dose of VNZ/TEZ/D-IVA was generally safe and well tolerated in subjects without CF who have moderate hepatic impairment and matched healthy volunteers. The PK results for VNZ/TEZ/D-IVA were similar in subjects with moderate hepatic impairment and matched healthy subjects.

In the controlled, Phase 3 studies (Studies 102 and 103) in CF subjects 12 years of age and older (Studies 102 and 103), 8 subjects with an ongoing medical history of portal hypertension, hepatic cirrhosis, and/or portal/hepatic fibrosis received VNZ/TEZ/D-IVA treatment. The safety data in these 8 subjects were generally consistent with the safety data in other subjects treated with VNZ/TEZ/D-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 VNZ/TEZ/D-IVA in this population is considered missing information.

SVII.3.3.4 Missing Information – Use in Children Aged 6 to 11 Years

Evidence source

In the open-label, Phase 3 Study 105, treatment with VNZ/TEZ/D-IVA for up to 24 weeks was generally safe and well tolerated in the completed Cohorts A1 and B1 evaluating CF subjects 6 through 11 years of age, and the safety results were consistent with the known safety profile. However, the study had a relatively small sample size of 95 subjects (17 subjects in Cohort A1 and 78 subjects in Cohort B1), and the overall safety experience is still limited. Therefore, the safety of VNZ/TEZ/D-IVA in this age group will need further characterisation.

Population in need of further characterisation

Safety of VNZ/TEZ/D-IVA treatment in children aged 6 to 11 years remains under ongoing evaluation in clinical studies and post-authorisation surveillance.

SVIII Summary of Safety Concerns

Important identified risks	• Hepatoxicity
Important potential risks	• Cataract
Missing information	• Use in pregnancy or breastfeeding • Long-term safety • Use in patients with moderate or severe hepatic impairment • Use in children aged 6 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 pregnancy or breastfeeding:

  The purpose of this questionnaire is to obtain structured information on the use of VNZ/TEZ/D-IVA in pregnancy and breastfeeding in the post-authorisation setting. A copy of the questionnaire is provided in Annex 4.

III.2 Additional Pharmacovigilance Activities

III.2.1 Open-label extension study in CF subjects ages 12 years and older *(Study 104)* is an ongoing Phase 3, open-label extension study evaluating the long-term safety, tolerability, and efficacy of VNZ/TEZ/D-IVA treatment for 96 weeks in subjects 12 years of age and older with CF who are homozygous for *F508del mutation* (F/F genotype), heterozygous for the *F508del mutation* and a gating, minimal, or residual function mutation (F/G, F/MF, or F/RF genotypes), or have at least 1 other triple combination responsive (TCR) CFTR mutation and no *F508del* mutation.

Rationale and Study Objectives:

- To evaluate the long-term safety and efficacy of VNZ/TEZ/D-IVA treatment in CF subjects 12 years of age and older.
- Safety concerns evaluated include:
  - Hepatotoxicity

- Cataract
- Long-term safety

Study Design: Phase 3, open-label extension study for subjects who completed the treatment period in the parent studies (Studies 102 and 103).

Study Population: Subjects 12 years of age and older with CF with F/F, F/MF, F/G, F/RF genotypes, or TCR CFTR mutation and no *F508del* mutation.

Milestones: 96 Week Report: 31 July 2026

III.2.3 Open-label extension study in CF subjects ages 1 to 11 years *(Study 106)* is an ongoing Phase 3, open-label extension study evaluating the long-term safety and efficacy of VNZ/TEZ/D-IVA treatment for 96 weeks in CF subjects 1 through 11 years of age with at least 1 TCR mutation (including *F508del*) in the CFTR gene.

Rationale and Study Objectives:

- To evaluate the long-term safety and efficacy of VNZ/TEZ/D-IVA treatment in CF subjects 1 year of age and older.
- Safety concerns evaluated include:
  - Hepatotoxicity
  - Cataract
  - Long-term safety
  - Use in children aged 6 to 11 years of age

Study Design: Phase 3, open-label extension study for subjects who completed the treatment period in the parent study (VX21-121-105, Part B).

Study Population: Subjects ages 1 through 11 years of age with CF with at least 1 other TCR mutation in the *CFTR* gene.

Milestones: 96 Week Report: 31 May 2030

III.2.4 Post-authorisation efficacy study *(PAES)* is a longitudinal, registry-based study to characterise the efficacy and safety of VNZ/TEZ/D-IVA in the treatment of CF in people aged 6 years and older who have at least one non-Class I mutation in the *CFTR* gene including people who have two non-*F508del* mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data).

Rationale and Study Objectives:

- To evaluate effectiveness / CF disease progression outcomes, safety outcomes, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking VNZ/TEZ/D-IVA in the real-word setting.
- Efficacy uncertainties evaluated include:
  - Efficacy in patients with 2 non-*F508del* mutations including *N1303K*, non-canonical splice, and mutations supported by FRT data only. Effectiveness / disease progression analyses endpoints include ppFEV$_1$, body mass index (BMI), and SwCl.
- Safety concerns evaluated include:
  - Hepatotoxicity
  - Use in pregnancy
  - Long-term safety

- Use in patients with moderate or severe hepatic impairment
- Use in children aged 6 to 11 years

Study Design: Post-authorisation, longitudinal study which will perform a within-cohort evaluation of outcomes in the 5-year periods before and after treatment, using data collected by existing national CF patient registries in Europe and the US.

Study Population: CF patients who have a record of treatment with VNZ/TEZ/D-IVA in the existing CF patient registries, regardless of age or genotype.

Milestones: Annual Reports: 31 December 2026/2027/2028/2029;

Final Report: 31 December 2030

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 7 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)				
Post-authorisation Efficacy Study (PAES) Planned	To characterise the efficacy and safety of VNZ/TEZ/D-IVA in the treatment of CF in people aged 6 years and older who have at least one non-Class I mutation in the *CFTR* gene including people who have two non-*F508del* mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data) by evaluating effectiveness / CF disease progression outcomes (including ppFEV$_1$, BMI, and SwCl), safety outcomes, frequency and outcome of pregnancy, and drug utilisation patterns in people taking VNZ/TEZ/D-IVA in the real-world setting	• Hepatotoxicity • Use in pregnancy • Long-term safety • Use in patients with moderate or severe hepatic impairment • Use in children aged 6 to 11 years	Annual Reports Final Report	31 December 2026/2027/2028/2029 31 December 2030
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)				
Open-label extension study in CF subjects ages 12 years and older (Study 104) Ongoing	**Primary Objective** • To evaluate the long-term safety and tolerability of VNZ/TEZ/D-IVA **Secondary Objective** • To evaluate the long-term efficacy of VNZ/TEZ/D-IVA	• Hepatotoxicity • Cataract • Long-term safety	96 Week Report	31 July 2026
Open-label extension study in CF subjects ages 1 to 11 years (Study 106) Ongoing	**Primary Objective** • To evaluate the long-term safety and tolerability of VNZ/TEZ/D-IVA **Secondary Objective** • To evaluate the long-term efficacy of VNZ/TEZ/D-IVA	• Hepatotoxicity • Cataract • Long-term safety • Use in children aged 6 to 11 years of age	96 Week Report	31 May 2030

BMI: body mass index; CF: cystic fibrosis; MA: market authorisation; PAES: post-authorisation efficacy study; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; PV: pharmacovigilance; Study 104: VX20-121-

Table 7 Planned and Ongoing Post-authorisation Studies in the Pharmacovigilance Plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates

104; Study 106: VX22-121-106; SwCl: sweat chloride; TEZ: tezacaftor; VNZ/TEZ/D-IVA: vanzacaftor in combination with tezacaftor and deutivacaftor

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				
Post-Authorisation Efficacy Study (PAES) Planned	To characterise the efficacy and safety of VNZ/TEZ/D-IVA in the treatment of CF in people aged 6 years and older who have at least one non-Class I mutation in the *CFTR* gene including people who have two non-*F508del* mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data) by evaluating effectiveness / CF disease progression outcomes (including ppFEV$_1$, BMI, and SwCl), safety outcomes, frequency and outcome of pregnancy, and drug utilisation patterns in people taking VNZ/TEZ/D-IVA in the real-world setting	Efficacy in patients with 2 non-*F508del* mutations including *N1303K*, non-canonical splice, and mutations supported by FRT data only	Protocol Submission	September 2025
			Start of data collection[a]	June 2026
			Interim Analyses	31 December 2026/2027/2028/2029
			End of data collection[a]	June 2030
			Final Study Report	31 December 2030
+--Efficacy studies which are Specific Obligations in the context of a conditional MA or a MA under exceptional circumstances				
None				

BMI: body mass index; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator gene; FRT: Fischer rat thyroid; MA: marketing authorisation; PAES: Post-Authorisation Efficacy Study; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

[a] Per EU Good Pharmacovigilance Practices VIII.A.1, the start of data collection in case of secondary use of data is the date from which data extraction starts and end of data collection is when the analytical datasets are completely available.

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

V.1 Routine Risk Minimisation Measures

Table 8 Routine Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Activities
Hepatotoxicity	**Routine risk communication:** SmPC Sections 4.4 and 4.8 PL Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measure to address the risk:

Table 8 Routine Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Activities
	Recommendations for LFT monitoring and treatment stopping rules are provided in SmPC Section 4.4. 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: Prescription only
Cataract	**Routine risk communication:** SmPC Sections 4.4 and 5.3 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: Recommendations for baseline and follow-up ophthalmologic examinations in paediatric patients are provided in SmPC Section 4.4. Expectations for eye examinations are discussed in PL Section 2.
	Other routine risk minimisation measures beyond the Product Information: Prescription only
Use in pregnancy or breastfeeding	**Routine risk communication:** SmPC Sections 4.6 and 5.3 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: Advice is given regarding use during pregnancy and breastfeeding in SmPC Section 4.6. 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: Prescription only
Long-term safety	**Routine risk communication:** None
	Routine risk minimisation activities recommending specific clinical measure to address the risk: None
	Other routine risk minimisation measures beyond the Product Information: Prescription only
Use in patients with moderate or severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2 and 5.2 PL Sections 2 and 3
	Routine risk minimisation activities recommending specific clinical measure to address the risk: Recommendations regarding use in patients with hepatic impairment are provided in SmPC Sections 4.2. 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: Prescription only
Use in children aged 6 to 11 years	**Routine risk communication:** SmPC Sections 4.1, 4.2, and 4.8 PL Sections 1 and 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: None
	Other routine risk minimisation measures beyond the Product Information: 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 9 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided. PL Sections 2 and 4 PL Sections 2 and 4 where expectations for LFT monitoring and detection of potential signs of liver problems are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study in CF subjects ages 12 years and older (Study 104) (96 Week Report: 31 July 2026) • Open-label extension study in CF subjects ages 1 to 11 years of age (Study 106) (96 Week Report: 31 May 2030) • PAES (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030)
Cataract	**Routine risk minimisation measures:** SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided. PL Section 2 PL Section 2 where expectations for eye examinations are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study in CF subjects ages 12 years and older (Study 104) (96 Week Report: 31 July 2026) • Open-label extension study in CF subjects ages 1 to 11 years of ages (Study 106) (96 Week Report: 31 May 2030)
Use in pregnancy or breastfeeding	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3 SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding. PL Section 2 PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up questionnaire **Additional PV activities:** • PAES (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030)

Table 9 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety	**Routine risk minimisation measures:** Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study in CF subjects ages 12 years and older (Study 104) (96 Week Report: 31 July 2026) • Open-label extension study in CF subjects ages 1 to 11 years of age (Study 106) (96 Week Report: 31 May 2030) • PAES (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030)
Use in patients with moderate or severe hepatic impairment	**Routine risk minimisation measure:** SmPC Sections 4.2 and 5.2 SmPC Sections 4.2 where recommendations regarding use in patients with hepatic impairment are provided. PL Sections 2 and 3 PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • PAES (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030)
Use in children aged 6 to 11 years	**Routine risk minimisation measure:** SmPC Sections 4.1, 4.2, and 4.8 PL Sections 1 and 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study in CF subjects ages 1 to 11 years of ages (Study 106) (96 Week Report: 31 May 2030) • PAES (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030)

CF: cystic fibrosis; LFT: liver function test; PL: Package Leaflet; PV: pharmacovigilance; PAES: post-authorisation efficacy study; Study 104: VX20-121-104; Study 106: VX22-121-106; SmPC: Summary of Product Characteristics; TEZ: tezacaftor

PART VI Summary of the RMP

Summary of Risk Management Plan for ALYFTREK (Vanzacaftor in Combination With Tezacaftor and Deutivacaftor)

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

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

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

I. The medicine and what it is used for

ALYFTREK is authorised for the treatment of cystic fibrosis (CF) in people aged 6◦years and older who have at least one◦non-Class I mutation in the CF transmembrane conductance regulator (CFTR) gene (see SmPC for the full indication). It contains vanzacaftor in combination with tezacaftor and deutivacaftor as the active substances and it is given orally.

Further information about the evaluation of ALYFTREK's benefits can be found in ALYFTREK's EPAR, including its plain-language summary, available on the EMA website under the medicine's webpage:

<Website hyperlink>.

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

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

Measures to minimise the risks identified for medicinal products can be

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

Together, these measures constitute *routine risk minimisation* measures.

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

II.A List of important risks and missing information

Important risks of ALYFTREK 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 ALYFTREK. 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	• Hepatotoxicity
Important potential risks	• Cataract
Missing information	• Use in pregnancy or breastfeeding

	• Long-term safety • Use in patients with moderate or severe hepatic impairment • Use in children aged 6 to 11 years

II.B Summary of important risks

Hepatotoxicity (Important identified risk)	
Evidence for linking the risk to the medicine	In the two 52 week, double-blinded, controlled Phase 3 pivotal studies (Studies 102 and 103) in CF subjects 12 years of age and older and the open-label, Phase 3 study (Study 105) in CF subjects 6 through 11 years of age, transaminase elevations have been reported. In some cases, a contributory role of ALYFTREK cannot be excluded. Based on the overall safety experience with ALYFTREK, hepatotoxicity is considered an important identified risk.
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 SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided. PL Sections 2 and 4 PL Sections 2 and 4 where expectations for LFT monitoring and detection of potential signs of liver problems are discussed. Prescription only
Additional pharmacovigilance activities	• Open-label extension study in CF subjects ages 12 years and older (Study 104) • Open-label extension study in CF subjects ages 1 to 11 years (Study 106) • Post-authorisation efficacy study (PAES) 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 12 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. As D-IVA is a deuterated isotopologue of ivacaftor, the potential risk of cataract is considered applicable to D-IVA containing regimen.
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 SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided. PL Section 2 PL Section 2 where expectations for eye examinations are discussed. Prescription only
Additional pharmacovigilance activities	• Open-label extension study in CF subjects ages 12 years and older (Study 104) • Open-label extension study in CF subjects ages 1 to 11 years (Study 106) See Section II.C of this summary for an overview of the post-authorisation development plan.
Use in pregnancy or breastfeeding (Missing information)	
Risk minimisation measures	SmPC Sections 4.6 and 5.3 SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding. PL Section 2 PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding. Prescription only
Additional pharmacovigilance activities	• Post-authorisation efficacy study (PAES) See Section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety (Missing information)	
Risk minimisation measures	Prescription only
Additional pharmacovigilance activities	• Open-label extension study in CF subjects ages 12 years and older (Study 104) • Open-label extension study in CF subjects ages 1 to 11 years (Study 106) • Post-authorisation efficacy study (PAES) 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 and 5.2 SmPC Sections 4.2 where recommendations regarding use in patients with hepatic impairment are provided. PL Sections 2 and 3 PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided. Prescription only
Additional pharmacovigilance activities	• Post-authorisation efficacy study (PAES) See Section II.C of this summary for an overview of the post-authorisation development plan.
• **Use in children aged 6 to 11 years**	
Risk minimisation measures	SmPC Sections 4.1, 4.2, and 4.8 PL Sections 1 and 2 Prescription only
Additional pharmacovigilance activities	• Open-label extension study in CF subjects ages 1 to 11 years (Study 106) • Post-authorisation efficacy study (PAES) See Section II.C of this summary for an overview of the post-authorisation development plan.

CF: cystic fibrosis; PL: Package Leaflet; PAES: post-authorisation efficacy study; SmPC: Summary of Product Characteristics; Study 102: VX20-121-102; Study 103: VX20-121-103; Study 104: VX20-121-104; Study 105: VX21-121-105; Study 106: VX22-121-106

II.C Post-authorisation development plan

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

Post-authorisation efficacy study (*PAES*)

Purpose of the study: To characterise the efficacy and safety of ALYFTREK in the treatment of CF in people aged 6 years and older who have at least one non-Class I mutation in the *CFTR* gene including people who have two non-*F508del* mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data).

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

Open-label extension study in CF subjects ages 12 years and older *(Study 104)*
Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of ALYFTREK for 96 weeks in CF subjects 12 years of age and older who are homozygous for *F508del* mutation (F/F genotype), heterozygous for the *F508del* mutation and a gating, minimal, or residual function mutation (F/G, F/MF or F/RF genotypes), or have at least 1 other triple combination responsive (TCR) CFTR mutation and no *F508del* mutation.

Open-label extension study in CF subjects ages 1 to 11 years *(Study 106)*

Purpose of the study: To evaluate the long-term safety and efficacy of ALYFTREK for 96 weeks in CF subjects 1 through 11 years of age with at least 1 TCR mutation (including *F508del*) in the *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

Pregnancy and Breastfeeding Questionnaire

- 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 Vanzacaftor/Tezacaftor/Deutivacaftor	
To:	, , ,
Site Contact:	Fax: ; Email:
Date:	
Re:	Patient: ; Manufacturer Control Number:
Reported Event(s):	

Patient Name/Initials *(recipient of drug)*:	DOB:	☐Female ☐Male Partner	**Maternal:** Age	Height cm / in	Weight kg / lb
Vertex Drug(s)	**Start Date**	**End Date**	**Dose, Frequency, Route**		
		☐Ongoing			
		☐Ongoing			
Pregnancy Outcome ☐Ongoing ☐Live Delivery ☐Spontaneous Abortion ☐Therapeutic Abortion ☐Elective Termination ☐Stillbirth ☐Unknown					
Infant Information ☐Female ☐Male	Date of Birth:	**APGAR** 1 min: 5 min:		Height cm / in	Weight kg / lb
Was an initial/baseline ophthalmologic examination performed for the infant at or shortly after birth? Yes ___ No ___ **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 <u>additional</u> contact information (e.g., OBGYN, Pediatrician):		
Has the patient <u>denied</u> 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)* ☐ Hospitalization Date of Admission: Discharge: ☐ Important Medical Event ☐ Life-threatening ☐ Permanent Disability ☐ Congenital Anomaly ☐ Death Date of Death:			**Event Outcome** ☐ Recovered / Resolved ☐ Recovering / Resolving ☐ Recovered / Resolved w Sequelae ☐ Not Recovered / Not Resolved (Ongoing) ☐ Fatal ☐ Unknown	
Vertex Drug(s)	**Related**	**Not Related**	**1**- Interrupted, **2**- Withdrawn, **3**- Not changed, **4**- Reduced, **5**- Not Applicable	
	☐	☐		
	☐	☐		
Alternative suspected etiology(ies):				
Narrative				

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

Infant Follow-up Information

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

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

Alternative suspected etiology(ies):
Narrative

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

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

Not applicable.

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