14 September 2023
EMA/CHMP/300920/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kaftrio

International non-proprietary name: Ivacaftor / Tezacaftor / Elexacaftor

Procedure No. EMEA/H/C/005269/X/0033

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Administrative information

Name of the medicinal product:	Kaftrio
MAH:	Vertex Pharmaceuticals (Ireland) Limited Unit 49 Northwood Court Block F2 Santry Dublin 9 IRELAND
Active substance:	Elexacaftor / Ivacaftor / Tezacaftor
International Non-proprietary Name/Common Name:	ivacaftor / tezacaftor / elexacaftor
Pharmaco-therapeutic group (ATC Code):	other respiratory system products, other respiratory system products (R07AX32)
Therapeutic indication(s):	Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see section 5.1).
Pharmaceutical form(s):	Granules
Strength(s):	60 mg / 40 mg / 80 mg and 75 mg / 50 mg / 100 mg
Route(s) of administration:	Oral use
Packaging:	sachet (BOPET/PE/Foil/PE)
Package size(s):	28 sachets

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List of abbreviations

Abbreviation	Term
BOPET	biaxially-oriented polyethylene terephthalate
CQA	Critical Quality Attribute
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
SDD	spray dried dispersion
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
XR(P)D	X-Ray (Powder) Diffraction
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC0-∞	AUC from the time of dosing extrapolated to infinity
BA	bioavailability
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised

CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
CK	creatine kinase
CL	clearance
Cmax	maximum observed concentration
DIOS	distal intestinal obstructive syndrome
ECG	electrocardiogram
ELX	elexacaftor
EU	European Union
F/F	homozygous for F508del
F/MF	heterozygous for F508del and a CFTR minimal function mutation
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDC	fixed-dose combination
FE-1	faecal elastase-1
FRT	Fisher Rat Thyroid
GGT	gamma-glutamyltransferase
ICH	International Council for Harmonization
IRT	immunoreactive trypsinogen
IVA	ivacaftor
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LS	least squares
LUM	lumacaftor
MBW	multiple-breath washout
MF	minimal function
MMRM	mixed-effects model for repeated measures
n	size of subsample
P	probability
PD	pharmacodynamic
PE	physical examination

PEx	pulmonary exacerbation
PK	pharmacokinetic
popPK	population PK
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	preferred term
q12h	every 12 hours
qAM	once every morning
qd	once daily
qPM	once every evening
RF	residual function
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SwCl	sweat chloride
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States

DEFINITION OF TERMS

All clinical study numbers conducted with elexacaftor (ELX; as monotherapy or combination therapy) are abbreviated to the last 3 digits (e.g., Study VX20-445-111 is Study 111).

Adverse Events

For the purpose of the safety analyses described herein, treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that worsened (either in severity or seriousness) or that were newly developed at or after the first dose date of the study drug through the end of the Treatment-emergent Period.

Unless otherwise specified, all TEAEs will be referred to as AEs in the text and tables.

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Ireland) Limited submitted on 22 November 2022 extensions of the marketing authorisation.

Extension application to add a new pharmaceutical form (granules) associated with 2 new strengths (60 mg/40 mg/80 mg and 75 mg/50 mg/100 mg) to support a new indication in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the CFTR gene (see section 5.1).

As a consequence of the line extension the PI for the film coated tablets is also updated to reflect the addition of a new pharmaceutical form.

The RMP (version 6.2) has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations

Kaftrio was designated as an orphan medicinal product EU/3/18/2116 on 14 December 2018 in the following condition: Cystic fibrosis that relates to the indication in the MAA.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Kaftrio as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here: kaftrio-orphan-maintenance-assessment-report-post-authorisation_en.pdf (europa.eu).

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0265/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002324-PIP01-17-M03 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: NA

PRAC Rapporteur: Martin Huber

The application was received by the EMA on	22 November 2022
The procedure started on	28 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 March 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 April 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	17 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	24 March 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	20 July 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	04 August 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kaftrio on	14 September 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Currently, Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The new claimed indication reads as follows:

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis conductance regulator (CFTR) gene.

Cystic fibrosis is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. CF is caused by mutations in the CFTR gene that result in an absent or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride channel responsible for regulating salt and water absorption and secretion. The failure to regulate chloride transport results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the CFTR protein results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration.

Lung disease is the primary cause of morbidity and mortality in people with CF.

F508del is the most common disease-causing mutation (84.7% of individuals in the US and 81.1% of individuals in Europe).

2.1.2. Epidemiology and screening tools

CF affects approximately 3,000 individuals in the US and a total of 54,000 in the EU in the registries included.[1,2] The number of adults with CF continues to increase, while the number of children remains relatively stable. In 2021, adults were 58.3 percent of the CF population, compared with 32.7 percent in 1991.[1] The incidence and prevalence of CF vary between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations. In the US, the median age at death was 33.9 years for the people with CF who were reported to have died in 2021. About 11 percent of deaths occurred before 20 years of age. A comparison of the cumulative percentage for age at death between 1991 and 2021 shows a substantial shift of the curve toward the right with a larger proportion of deaths occurring at older ages. For individuals born between 2017 and 2021, the median predicted survival age was 53.1 years (95 percent confidence interval: 51.6 - 54.7 years).

2.1.1. Aetiology and pathogenesis

The CFTR protein is an epithelial chloride ion (Cl-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, responsible for aiding in the regulation of salt and water absorption and secretion. More than 2000 mutations in the CFTR gene have been identified.

[1] Annual Data Report 2021 Cystic Fibrosis Foundation Patient Registry
[2] European Cystic Fibrosis Society. 2021 ECFS Patient Registry Annual Data Report

CFTR mutations can be classified according to the mechanisms that disrupt CFTR function.

• Class I mutations: Defective protein production

• Class II mutations: Defective protein processing

• Class III mutations: Defective regulation

• Class IV mutations: Defective chloride conduction

• Class V mutations: Reduced amounts of functional CFTR protein (less transcription)

Class I, II and III usually lead to a classic (severe) CF phenotype with pancreatic insufficiency.

Class IV and V are mostly associated with a milder expression of the disease.

The most prevalent mutation is an in-frame deletion in the CFTR gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR), which is considered a Class II mutation: it prevents most of the CFTR protein from reaching the cell surface, resulting in little-to-no chloride transport. The decrease in the amount of F508del-CFTR at the cell surface is due to a defect in the processing and trafficking of the F508del-CFTR protein. The very small amount of F508del-CFTR protein that reaches the cell surface also has defective channel gating and decreased stability at the cell surface. Patients who are homozygous with F508del-CFTR defects have little or no CFTR protein at the cell surface and hence suffer from a severe form of CF disease.

More than 2000 mutations of the CFTR gene have been identified. Most of the CFTR gene mutations are not associated with CF disease or are very rare. Currently, the CFTR2 database (an online resource that provides clinical and nonclinical data about CF-associated CFTR mutations) contains information on 412 of these identified mutations, with sufficient evidence to define 346 mutations as disease-causing.

CF-causing mutations can be divided into 2 groups based on the extent of loss of chloride transport caused by the mutation. In general, a complete or near-complete loss of CFTR chloride is referred to as "minimal function" of CFTR (class I, II and III). A residual CFTR-mediated chloride transport is referred to as "residual function" of CFTR (class IV and V).

2.1.2. Clinical presentation, diagnosis and stage/prognosis

CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF. Progressive loss of lung function is the leading cause of mortality. The clinical manifestations are those of progressive airway obstruction and bronchiectasis, with periods of worsening pulmonary symptoms associated with a decline in pulmonary function and increased bacterial density in airway secretions (pulmonary exacerbations). Obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. In addition, poor growth and nutritional status have historically been common in patients with CF owing to a number of factors, including pancreatic insufficiency-related fat malabsorption, increased energy expenditure attributable to progressive lung disease, appetite suppression attributable to chronic infection, and CF-related diabetes. These signs and symptoms are the typical manifestations of CF, and generally occur in advanced form in older paediatric and adult CF patients. However, less severe form of the above-mentioned manifestations of

the disease can be observed in early childhood or – in patients with severe genotypes (with gating mutations such as *G551D*) – in infancy or even in utero. In CF patients with gating mutations pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement, manifested by pulmonary inflammation and infection, begins shortly after birth.

Exocrine pancreatic insufficiency and poor nutritional status are among the most significant clinical manifestations of CF in infants with severe genotypes. These factors often lead to poor growth with subsequent growth delay, poorer cognitive development, and are associated with other clinical comorbidities such as decreased lung function and decreased survival. Malnourishment is associated with worsening lung function in children with CF and is an independent predictor of mortality in this population. In one study, fat malabsorption was present in 79% of infants tested at 6 months and 92% of infants by 12 months of age. Additionally, increased energy expenditure and appetite suppression due to lung disease contribute to poor somatic growth and poor nutritional status in young patients with CF.

Since the introduction and continued advances of newborn and antenatal screening, many patients with CF are identified through a positive screening test and subsequently diagnosed within the first year of life. Approximately 65% of patients in the ECFSPR 2020 Annual Report are diagnosed by 1 year of age, with a median (min., max.) age at diagnosis of 0.30 (0.00, 82.57) years. Data in the literature suggest that early therapeutic intervention is beneficial to children with CF; studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed by newborn screening. Therefore, it is expected that the initiation of treatment with CFTR modulators targeting the functional defects of the mutated CFTR protein could postpone or even prevent the onset of clinical manifestations of cystic fibrosis such as lung disease and impaired exocrine pancreatic function

In Europe, the median age of all CF patients was 18.5 years (with the youngest patient being diagnosed just after birth and the oldest patients being 88.4 years of age) in 2017. Despite advances in treatment, the current median age of death in a patient with CF is approximately 31 years. In 2018, the median predicted survival age of those born in 2018 was 47.4 years (95% CI: 44.2–50.3 years)[1]. Such a prediction assumes no further improvement in mortality rate and thus does not consider the potential impact of CFTR modulators and other improvements in clinical care.

CF is diagnosed when both of the following criteria are met:

- Clinical symptoms consistent with CF in at least one organ system (CLASSIC), or positive newborn screening or genetic testing for siblings of patients with CF

AND

- Evidence of CFTR dysfunction (any of the following):
    - Elevated sweat chloride $\geqslant$60 mmol/L (CLASSIC)
    - Presence of two disease-causing mutations in CFTR, one from each parental allele
    - Abnormal nasal potential difference

Around 2 % of patients lack one or more of the "CLASSIC" features. They may have milder clinical symptoms and/or normal to intermediate sweat chloride results. These patients can still be diagnosed with CF if they meet genetic or functional criteria.

2.1.3. Management

Existing treatments for CF can be broadly classified into 2 groups: (1) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy) and (2) CFTR modulators (i.e., correctors and potentiators) which target the underlying cause of the disease. Concomitant administrations of these two groups are recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

(1) CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. These therapies are predominantly generic medicines authorized at a national level, apart from agents for the management of chronic pulmonary infections due to Pseudomonas aeruginosa.

(2) CFTR modulators are small molecules that target specific defects caused by mutations in the CFTR gene. Correctors (tezacaftor, lumacaftor and elexacaftor) facilitate the cellular processing and trafficking of CFTR to increase the quantity of CFTR at the cell surface. Potentiators (ivacaftor) increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance chloride transport. A combination of a corrector and a potentiator should result in sufficient levels of CFTR at the surface, which is then enhanced for its gating function. Kaftrio (elexacaftor, tezacaftor/ivacaftor), Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA), and Symkevi (tezacaftor/ivacaftor, TEZ/IVA) are CFTR modulators approved for CF patients with specific mutations.

It is believed that if a CFTR modulator regimen had a large enough effect on F508del-CFTR, then the presence of a single F508del allele alone would be sufficient to derive significant clinical benefit. That single regimen would be effective in all patients with at least one F508del allele, regardless of the mutation on the second allele. If the second allele is also responsive, any benefit derived from that allele would be in addition to the benefit derived from the effect on F508del-CFTR. Importantly, for patients who have one F508del allele and are currently being treated with CFTR modulators (i.e. F/G and F/RF patients), their F508del allele seems not being fully leveraged because approved regimens primarily target the gating (IVA) or RF (IVA and TEZ/IVA) allele with limited modulation of the single F508del allele; these patients too would benefit from additional, highly effective modulation of their F508del.

2.2. About the product

Kaftrio belongs to the pharmacotherapeutic group of other respiratory system products with ATC code R07AX32. Kaftrio is a triple combination product that contains the CFTR modulators elexacaftor, ivacaftor and tezacaftor.

Tezacaftor, as CFTR corrector, facilitates the cellular processing and trafficking of CFTR (including F508del-CFTR) to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor, as a CFTR potentiator, potentiates the channel- open probability (or gating) of CFTR at the cell surface to increase chloride transport. Elexacaftor, as a next-generation CFTR corrector, also facilitates the cellular processing and trafficking of CFTR. The product is considered to have a different chemical structure and a different mechanism of action as the first generations of CFTR correctors (TEZ, LUM) and potentiator (IVA).

The combination of elexacaftor, tezacaftor and ivacaftor results in increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency.

Kaftrio is already registered for patients aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

2.3. Type of Application and aspects on development

This application is an extension of the marketing authorisation to add a new pharmaceutical form including a new indication.

Currently, the applicant is applying to register the addition of a new oral granules in sachet dosage form of the triple combination of elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA), grouped with a Type II variation to expand the indication of KAFTRIO to patients aged 2 to less than 6 years.

The two proposed dosing strengths for KAFTRIO granules are (1) ELX/TEZ/IVA 100/50/75 mg fixed-dose combination (FDC) granules, and (2) ELX/TEZ/IVA 80/40/60 mg FDC granules.

For the proposed use in paediatric patients aged 2 to less than 6 years, the age- and weight-adapted dosing of ELX/TEZ/IVA combinations therapy is proposed as follows:

Table 1 Dosing recommendations for patients aged 2 to less than 6 years

Age	Weight	Morning dose	Evening dose
2 to less than 6 years	<14 kg	One sachet of ivacaftor 60 mg/tezacaftor 40 mg/ elexacaftor 80 mg granules	One sachet of ivacaftor 59.5 mg granules
	≥14 kg	One sachet of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg granules	One sachet of ivacaftor 75 mg granules

The dose is to be taken approximately 12 hours apart. Both Kaftrio and ivacaftor tablets should be taken with fat-containing food. Examples of meals or snacks containing fat are those prepared with butter or oils or eggs, cheeses, nuts, whole milk, or meats.

In the development of Kaftrio "minimal function" mutations (MF) are defined as mutations that produce (1) no CFTR protein or (2) a CFTR protein that is not responsive to IVA and TEZ/IVA in vitro (comparable to Class I).

The populations described in the report are according to the definitions in the clinical development of Kaftrio:

- Homozygous for F508del (F/F)
- Heterozygous for F508del and a minimal function mutation (F/MF)
- Heterozygous for F508del and a gating mutation (F/G)
- Heterozygous for F508del and a residual function mutation (F/RF)

2.4. Quality aspects

2.4.1. Introduction

The scope of this application is to introduce a new pharmaceutical form, granules in sachet, in 2 strengths, in addition to the already authorised film coated tablets, to support an extension of indication to paediatric patients.

The finished product is presented as granules in sachet in 2 strengths containing 60 mg of ivacaftor, 40 mg of tezacaftor and 80 mg of elexacaftor , or 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor, as active substances.

Other ingredients are colloidal anhydrous silica (E551), croscarmellose sodium (E468), hypromellose, hypromellose acetate succinate, lactose monohydrate, magnesium stearate (E470b), mannitol (E421), sodium laurilsulfate, and sucralose (E955).

The product is available in biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE) printed foil laminate sachet, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The finished product contains three active substances: ivacaftor, tezacaftor and elexacaftor. The granules in sachet are a line extension of the already authorised product Kaftrio film-coated tablets containing the same active substances. No module 3.2.S has been submitted for this line extension.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished products consists of white to off-white, sweetened, unflavoured immediate-release granules for oral administration. The granules are a fixed-dose combination (FDC) of the active ingredients ivacaftor, tezacaftor and elexacaftor. Both ivacaftor and tezacaftor active substances are included in the formulation as amorphous spray-dried dispersion (SDD) intermediates, whereas elexacaftor is provided as crystalline solid. This is the same as in the authorised Kaftrio tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur., USP and USP/NF standards with the exception of a process solvent, removed during the manufacturing process, which is controlled to an in-house standard. There are no novel excipients used in the finished product formulation. The list of excipients is listed in Section 6.1 of the SmPC.

Granules have a nominal diameter of 2 mm and an approximate thickness of 2 mm. The granules are filled by count into the primary container (single dose foil sachet) to the target strength. For administration, the granules are emptied from the sachet and mixed with a small amount of soft food.

The granules formulations have been developed for use in children. Due to the low aqueous solubility of ivacaftor and insufficient stability of the amorphous ivacaftor in aqueous media, neither a solution nor a suspension formulation is feasible. Therefore, a granule dosage form was developed for ease of administration.

The formulation development was mainly based on the existing Kalydeco (ivacaftor) granules from the same MAH. All excipients are well known pharmaceutical ingredients. All excipients used in Kaftrio granules are also used in Kaftrio tablets with exception of mannitol and sucralose, which were added to enhance the sensory attributes and palatability of the formulation when mixed with soft foods, as was done for Kalydeco granules.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Chemical and physical compatibility of the active substances with the excipients was confirmed by placing the granules in an open dish study at 40 °C/ 75% RH for 3 months.

Both granules strengths are manufactured from the same compression blend/granules. The amount of granules filled into the sachet makes up the strength of the product.

A detailed discussion on the age-appropriateness of the finished product for use in children of 2-6 years in line with the Guideline on pharmaceutical development of medicines for paediatric use was not provided in the quality part of the dossier. However, no direct safety issues are foreseen with regard to the excipients and their quantities in the formulation for use in children. All excipients have been used previously in the intended age group (i.e. Kalydeco granules). Furthermore, the proposed Kaftrio granules are the same size as the approved Kalydeco granules and are indicated for use in children from 4 months of age; hence no difficulties with swallowing are expected.

The palatability of the granules and the formulation was developed to perform similarly to the tablets. The granules will be dosed in a small amount of food. The compatibility of the finished product with different foods has been demonstrated in P.2.6. Briefly, chemical and physical stability of granules mixed with small volumes (~5 mL) of selected liquids and soft foods were evaluated by testing assay, degradation products, dissolution, and physical form. The results at 2 hours after mixing the Kaftrio granules with water, apple juice, carrot puree, and whole milk yogurt demonstrated acceptable chemical stability. The results support the administration of the granules in food.

Therefore, in the SmPC it is described that the entire contents of one sachet should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. A statement on the stability of one hour after mixing is included as well. These instructions are the same as for the Kalydeco granules and are acceptable.

The batches used in the clinical studies were manufactured according to the finalized manufacturing process and composition and are representative for the commercial product.

The proposed dissolution methods for ivacaftor, tezacaftor and elexacaftor are based on the dissolution methods for the three active substances in the Kaftrio tablets. The proposed dissolution methods are acceptable.

Extensive studies have been carried out to demonstrate the discriminatory power of the methods. Discriminatory power has been shown for the dissolution methods for elexacaftor and tezacaftor. Although the ivacaftor dissolution method was not shown to be able to discriminate with respect to the studied changes in granules material/granule attributes and process parameters, the same dissolution method has been approved for the currently registered Kaftrio tablets and therefore is accepted.

Product and process development was conducted under a Quality by Design (QbD) paradigm. The QTPP is shown below:

Table 2: Quality Target Product Profile for Kaftrio granules

Safe and efficacious
Bioavailable
Oral administration of granules dispersed in liquid/soft food
One sachet containing immediate release fixed-dose combination granules with either ELX/TEZ/IVA 100/50/75 mg or 80/40/60 mg
Dosing frequency QD (for the morning dose)
At least 24 month shelf-life at room temperature packaged in sachets

The ELX/TEZ/IVA granules CQAs for the granules are: appearance, identification, assay, degradation products, dissolution, content uniformity, physical form, residual solvents, microbial attributes, elemental impurities, and chiral purity

The manufacturing process development and development studies performed were guided by an initial risk assessment where the potential impact of material attributes and process steps that could potentially impact the CQAs were evaluated.

QbD experiments have been performed for several manufacturing steps. DOEs were subsequently used to design multivariate experiments to evaluate main effects and interactions on the CQAs. These experiments considered the desired manufacturing range (DMR) as well as incoming material specification and equipment capability. Experimental designs were conducted for the blending, lubrication, and compression unit operations. Information on in-process controls has been supplied.

The primary packaging is a biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE) printed foil laminate sachet. The materials comply with Commission Regulation (EU) No 10/2011 for food contact materials. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The granules are manufactured by a direct compression process. The manufacturing process comprises three steps: blending blending, compression and sachet filling. The manufacturing process is a standard process.

The manufacturing process has been described in sufficient detail including the equipment type(s) for each unit operation, equipment working capacity, where appropriate, and process parameters (CPP and non-CPP) along with their target values or ranges.

An adequate criticality analysis was performed as part of the pharmaceutical development. Sufficient information on the control of critical steps has been provided in the dossier and the in-process acceptance limits have been justified. A design space has been developed for the compression stage of the process The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Major steps of the manufacturing process have been validated by a number of studies. A process validation scheme has been included in 3.2.R. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (IR), assay (HPLC), degradation products (HPLC), content uniformity (Ph. Eur.), dissolution (Ph. Eur.), water content (Karl Fischer), microbial limits (TAYMC, TYMC, *E.coli*) (Ph. Eur.).

The specified organic impurities in the granules are degradation products of elexacaftor. The acceptance criterion for one of the specified impurities is supported by a toxicology study. The acceptance criterion for additional specified and unspecified degradation products are in line with ICH Q3B.

The specified impurities and other degradation products have not been observed above the ICH reporting threshold of 0.1% w/w throughout finished product development, release testing and stability.

Acceptable justifications for omitting tests for the physical form, chiral purity, residual solvents, elemental impurities, and nitrosamines in the finished product specification have been provided.

The elemental impurities risk assessment concluded that content of Class 1 and Class 2A elemental impurities is consistently below 30% of the ICH Q3D (R2) Option 1 limits for all three active substances, confirmed by testing. Furthermore, it concluded that content of Class 1 and Class 2A elemental impurities is below 30% of the ICH Q3D (R2) Option 1 limits for all granule excipients with the exception of colloidal silicon dioxide. For colloidal silicon dioxide, the Option 2b summation approach was employed to demonstrate that the maximum daily intake of each Class 1 and Class 2A elemental impurity is well below 30% of its respective permitted daily exposure. Confirmatory testing results on seven representative clinical batches and three representative development batches of Kaftrio granules in sachet were in alignment with the risk assessment. The risk assessment also demonstrated that control limits for elemental impurities intentionally added in the elexacaftor, tezacaftor and ivacaftor active substances manufacturing processes are sufficient to ensure that the finished product will conform to ICH Q3D (R2) requirements. Therefore, no additional controls on elemental impurities in the granules finished product are required.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the finished product. Therefore, no specific control measures are deemed necessary.

The proposed finished product specification is acceptable.

Analytical procedures and reference standards

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis

Batch analysis results from three pilot scale batches of each of the proposed strengths (60 mg/40 mg/80 mg and 75 mg/50 mg/100 mg) and a 30mg/20mg/40 mg strength (not proposed for marketing authorisation) were presented. Additional batch analysis data from two commercial scale batches of the

75 mg/50 mg/100 mg strength, and one commercial scale batch from the 60 mg/40 mg/80 mg and 30mg/20mg/40 mg strengths were also provided. The data confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

The proposed shelf life of Kaftrio granules is 24 months.

This is supported by the following:

• Twelve months data from three pilot scale primary stability batches of Kaftrio 75 mg/50 mg/100 mg granules stored at long term (25°C/60% RH) and intermediate (30°C/75% RH) conditions and six months at accelerated (40°C/75% RH) conditions

• Twelve months data from one pilot scale primary stability batch of Kaftrio 60 mg/40 mg/80 mg granules stored at long term (25°C/60% RH) and intermediate (30°C/75% RH) conditions and six months at accelerated (40°C/75% RH) conditions

• Twelve months data from three pilot scale primary stability batches of Kaftrio 30mg/20mg/40 mg (not proposed for marketing authorisation) stored at long term (25°C/60% RH) and intermediate(30°C/75% RH) conditions and six months at accelerated (40°C/75% RH) conditions

• One (1) month of accelerated stability data from three supportive stability batches (one batch from each strength)

Samples were tested for appearance, assay, degradation products, chiral purity, dissolution, XRPD physical form, KF water content, water activity, and microbiological quality.

Stability studies are carried out under ICH conditions and the tested parameters are considered stability indicating. The batches were stored in the commercial sachet. The bracketing design is acceptable. No significant changes or trends have been identified at any storage condition.

The post-approval stability protocol and the stability commitment are considered acceptable[1].

Photostability per ICH Q1B, Option 2, was not performed with Kaftrio granules as the commercial container closure is light protective. Nonetheless, forced degradation studies were performed, which confirmed that the product is not sensitive to light.

As indicated above the entire contents of one sachet should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. Once mixed, the mixture is stable for one hour. These instructions are the same as for the Kalydeco granules and therefore acceptable.

Based on available stability data, the proposed shelf-life of 2 years stored as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The development Kaftrio granules is largely based on the development of the authorised Kaftrio tablets and the Kalydeco granules (from the same MAH). Information on development, manufacture and control of the granules has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. Design space have been proposed for several steps in the manufacture of the active substance and finished product. The design spaces have been adequately verified. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

The applicant did not submit non-clinical studies supporting the new indication in the paediatric population but referred to previously submitted data. The previously conducted juvenile data were submitted again in this procedure upon request from CHMP.

2.5.2. Summary of previous data submitted related to juvenile and PK studies

Two non-GLP dose range finding (DRF) studies and a PK study focussing on brain distribution with tezacaftor, and a pivotal GLP juvenile toxicity study with tezacaftor and ivacaftor were submitted in a previous variation procedure and in the renewal procedure for Symkevi.

In summary, the pivotal study in rats dosed from post-natal day (PND) 21-49 did not show toxicity at the highest dose, approximately two times the intended human exposure. However, in one of the DRFs it was observed that the dose directly above the NOAEL with a 4-fold exposure margin to human resulted in lethality of the pups. A PK distribution study showed that lower brain levels of P-glycoprotein (P-gp) activity in younger rats was associated with higher brain concentrations of tezacaftor and M1-TEZ. Although not relevant for the human population of 6 years and older, relevance of this finding cannot be excluded for the younger population 2 years and older.

2.5.3. Environmental Risk Assessment

The environmental risk assessments for ivacaftor and tezacaftor are finalised. For elexacaftor, a phase II tier B assessment is currently pending and studies are ongoing.

The prevalence data are used in the Phase I studies to determine the exposure for each active substance included the prevalence of cystic fibrosis in all patients, irrespective of age. Consequently, there will be no increase in environmental exposure to ivacaftor, tezacaftor and elexacaftor from the extension of the

indication to the 2 to 5 age group. No additional ERA studies, beyond the planned Phase II Tier B risk assessment for VX-445 (elexacaftor), need to be conducted to support this submission.

2.5.4. Discussion on non-clinical aspects

In the current procedure, the juvenile studies are considered very relevant since dosing in the juvenile rat studies occured from the post-natal day (PND) 21 or earlier, which corresponds to a human age of about 2 years

A discussion on the safety of Kaftrio in a juvenile population from 2 years of age was required by CHMP including the findings from pivotal and DRF studies, where lethality was seen in animals dosed from PND21 with only a 4-fold exposure margin, P-pg expression maturation differences between humans and rats, substrate affinity differences between P-gp for both species, and brain exposure to tezacaftor and M1-TEZ.

The MAH provided findings from the DRF and TK profiling studies and concluded that neurotoxicity of tezacaftor in juvenile animals is related to P-gP expression levels in rats. Consequently, the timing and dosing were adjusted towards the P-gP expression maturation in rats. It can be agreed that it is very likely that juvenile toxicity of tezacaftor is related to the functionality of P-gP in rats and that this might also be the case in humans. It should be noted that the maturation of expression and functionality of animal transporters cannot be translated to humans. The MAH, based on a study from Lam et al. (2015) on the expression levels of P-gP in humans, concludes that expression levels are mature within 3-6 months after birth. Consequently, the MAH argues that the effects observed in rats are not relevant for children aged 2-6 years old. However, Nicolas and de Lange* (2019) was critical on the methods and design of the study conducted by Lam et al. Furthermore, they refer to some clinical (functional) data on experience with P-gP substrates suggesting that expression is not necessarily equally translated to the functionality of P-gP. Also, data on the functionality of P-gP in rhesus monkeys suggest maturation around 9 months, which would correlate to 1-2 years old infants. Therefore, the argument of the MAH that P-gP is at mature levels in infants 3-6 months old was not endorsed by CHMP.

Therefore, the MAH proposed statement in section 5.3 of the SmPC for tezacaftor(*These findings are not relevant for the indicated paediatric population 2 years of age and older, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults.)* was considered not adequate by CHMP as not sufficiently based on data. A more cautious statement was requested and agreed as follows:

These findings are likely not relevant for the indicated paediatric population 2 years of age and older, for whom levels of P-glycoprotein expression levels are equivalent to levels observed in adults.

Finally, elexacaftor /tezacaftor/ivacaftor are not PBT substances. Considering the above data, elexacaftor /tezacaftor/ivacaftor is not expected to pose a risk to the environment.

2.5.5. Conclusion on non-clinical aspects

The section 5.3 of the SmPC has been updated with the CHMP above recommended statement which is now acceptable.

There is uncertainty regarding the relevance of the effects observed in juvenile rats, particularly convulsions and lethality seen at doses of 4-fold human exposure. Furthermore, the CHMP considered that the data supporting for the safe use of tezacaftor and Kaftrio in young children would primarily be based on clinical data.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A pivotal study, Study 111, a Phase 3, open-label, 2 part (Parts A and B), multicentre study was conducted in subjects 2 through 5 years of age. Part A evaluated the PK, safety, and tolerability of ELX/TEZ/IVA administered for 15 days to confirm a dose for Part B. Part B evaluated the safety, tolerability, PK, PD, and efficacy of ELX/TEZ/IVA administered for 24 weeks.

Additionally, a BA study, Study 012, was conducted in healthy adult subjects to support the use of granules in Study 111 in CF subjects 2 through 5 years of age. The ELX 100-mg/TEZ 50-mg/IVA 75-mg FDC tablet used in Study 012 is the same formulation approved for use in patients ⩾12 years of age and patients ⩾6 years of age who weigh ⩾30 kg.

Additionally, a sensory study, Study 013, was conducted in healthy adult subjects to evaluate the sensory attributes of the oral granules.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Study 111 Part A evaluated the PK of ELX, TEZ, and IVA in subjects 2 through 5 years of age as a primary objective. PK was a secondary objective in Study 111 Part B to assess whether target exposures previously shown to be safe and efficacious in older children and adults were achieved with the dosing regimens evaluated. To minimize the amount of blood collected in the paediatric subjects, sparse PK sampling was used during Study 111, and a popPK modelling approach was used to describe the exposures of the three drugs in children aged 2-5 years. Previously developed popPK models that described the PK of ELX, M23-ELX, TEZ, M1-TEZ and IVA in CF adults, adolescents, 6-11y subjects were updated with the final data from Study 111 and used to describe the exposures in children 2-5 years of age.

Body weight was the only covariate found to have a clinically meaningful impact on ELX, M23-ELX, TEZ, M1-TEZ and IVA disposition in subject 2 through 5 years of age. Overall, the final models demonstrated suitability for the simulations.

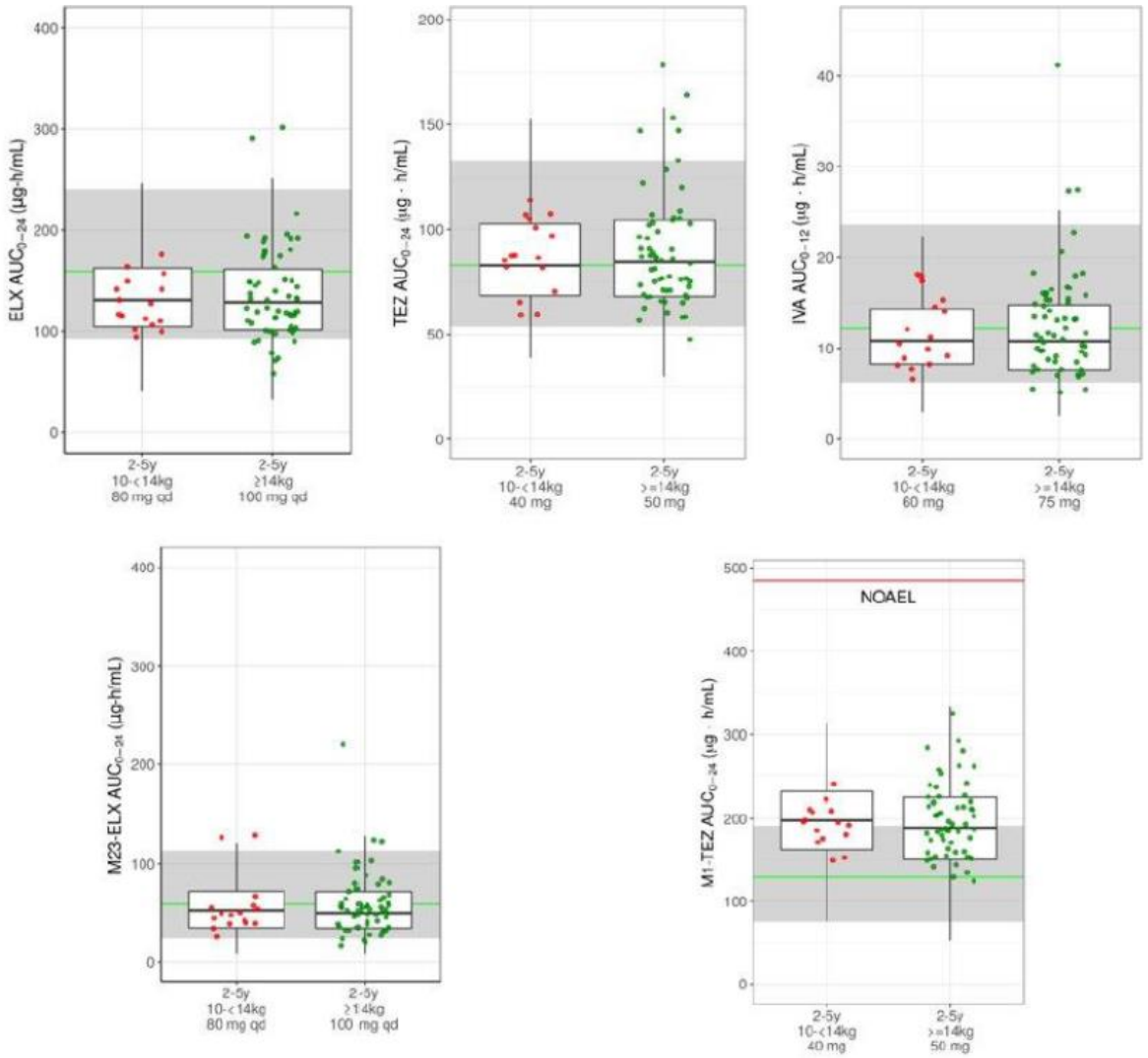
The simulations results demonstrated that under the studied dosing regimen with a 14 kg weight cutoff, the exposures were within the 5th to 95th percentile of the observed exposure range for subjects ≥18 years of age for both weight groups, although the median of the ELX exposures was below of the median seen in adults, (see Figure 2 below). M23-ELX exposures in some subjects 2 through 5 years of age who weighed ≥14 kg were outside the 5th to 95th percentile of the observed exposure range for subjects ≥18 years of age from Studies 102 and 103. These exposures are below the maximum steady-state AUC of 332 µg·h/mL observed from Study 104 (ELX 200 mg qd/TEZ 100 mg qd/ IVA 150 mg q12h), and thus are within the adult exposure range previously shown to be safe and efficacious.

The majority of TEZ exposures were within the 5th and 95th percentile of the observed exposure range for subjects ≥18 years of age for each weight group. The individual M1-TEZ exposures for subjects 2 through 5 years of age were higher than the M1-TEZ exposures in subjects ≥18 years of age but lower on a mean level

than the M1-TEZ exposures in subjects 6 through 11 years of age weighing ≥30 kg who received the adult dose (see Table 3). The range of M1-TEZ exposures for subjects 2 through 5 years of age is also generally below the maximum steady-state AUC observed from previous clinical studies of ELX/TEZ/IVA (Studies 102, 103, 104, and 106).

Overall, it can be concluded that in subjects 2 through 5 years of age, the majority of ELX, TEZ, and IVA exposures were within the exposure range observed for subjects ≥18 years of age for each weight group.

Figure 1: Summary of Steady-state AUC by Age Group for ELX, TEZ, IVA, and Metabolites.



Source: Report S054/Figure 6-18 (ELX and M23-ELX), Report S055/Figure 65 (TEZ), Figure 134 (M1-TEZ), and Figure 201 (IVA)

EBE: empirical Bayes estimate; ELX: elexacaftor; IQR: interquartile range; IVA: ivacaftor; NOAEL: No-observed-adverse-effect level; TEZ: tezacaftor; y: years of age

Notes: Boxplots represent simulations of virtual subjects randomly sampled from the 2-5y CF subjects in Study 111 Part B administered the studied dosing regimen. Median values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to the largest and smallest values within 1.5×IQR. Marker lines: green line represents median of the adult values; gray shaded area indicates 5th and 95th percentiles of the adult values. Points represent individual exposures based on the individual EBE values from 2-5y subjects in Study 111 Part B.

Table 3: Summary of Steady-State Exposures in different age groups

Age Group, Weight	Dose Regimen (ELX/TEZ/IVA)	ELX AUC_{0-24h} (µg·h/mL)			M23-ELX AUC_{0-24h} (µg·h/mL)			TEZ AUC_{0-24h} (µg·h/mL)			M1-TEZ AUC_{0-24h} (µg·h/mL)			IVA AUC_{0-12h} (µg·h/mL)		
		N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
2 through 5 years	(both doses combined)	75	136 (43.3)	59.2, 301	75	58.5 (31.9)	16.9, 220	75	89.6 (25.9)	47.5, 178	75	197 (39.8)	125, 326	75	12.8 (5.70)	5.15, 41.2
10 to <14 kg	80 mg qd/40 mg qd/60 mg qAM and 59.5 mg qPM	16	128 (24.8)	94.3, 176	16	56.5 (29.4)	25.7, 128	16	87.3 (17.3)	59.3, 114	16	194 (24.8)	150, 240	16	11.9 (3.86)	6.57, 18.1
≥14 kg	100 mg qd/ 50 mg qd/ 75 mg q12h	59	138 (47)	58.4, 302	59	59 (32.7)	16.9, 220	59	90.2 (27.9)	47.5, 178	59	197 (43.2)	125, 326	59	13.0 (6.11)	5.15, 41.2
6 through 11 years	(both doses combined)	66	154 (64)	61.6, 317	66	71.6 (48.8)	17.4, 206	66	87.3 (30.0)	43.5, 158	66	178 (48.0)	84.2, 280	66	13.6 (7.12)	3.73, 43.0
<30 kg	100 mg qd/ 50 mg qd/ 75 mg q12h	36	118 (39.8)	61.6, 247	36	45.3 (25.2)	17.4, 129	36	71.2 (23.9)	43.5, 155	36	149 (34.8)	84.2, 242	36	10.2 (6.63)	3.73, 43.0
≥30 kg	200 mg qd/ 100 mg qd/ 150 mg q12h	30	198 (60.7)	97.5, 317	30	103 (51.8)	18.2, 206	30	107 (24.9)	57.7, 158	30	214 (35.7)	134, 280	30	17.6 (5.47)	9.11, 27.5
12 through 17 years	200 mg qd/ 100 mg qd/ 150 mg q12h	72	146 (38)	64.5, 258	71	60 (26.2)	12.3, 133	69	89.0 (23.8)	46.5, 155	69	154 (36.7)	73.6, 248	69	11.6 (5.01)	4.41, 31.4
≥18 years	200 mg qd/ 100 mg qd/ 150 mg q12h	179	164 (51.1)	69, 392	179	65.7 (29.4)	13.4, 152	186	86.8 (26.5)	32.8, 211	186	131 (35.5)	22.9, 219	186	13.3 (5.34)	3.60, 33.4

Sources: Report S054/Tables 6-9 and 6-10; Report S055/Tables 6, 14, and 22
ELX: elexacaftor; IVA: ivacaftor; M1-TEZ: metabolite of TEZ; M23-ELX: metabolite of elexacaftor; N: total sample size; q12h: every 12 hours; qAM: every morning; qd: once daily; qPM: every evening; TEZ: tezacaftor

Bioequivalence

Study 012 was a Phase 1, open-label, randomized, 2-sequence, 2-period crossover study to evaluate relative BA of an ELX 100 mg/TEZ 50 mg/IVA 75 mg FDC granule formulation compared to a reference ELX 100 mg/TEZ 50 mg/IVA 75 mg FDC tablet formulation.

Exposures of ELX were approximately 18% to 19% lower after administration of the FDC granules relative to the reference FDC tablet in study 012. However, the 90% CIs fell within the pre-specified bounds of 0.7 and 1.43, and the difference was deemed not clinically relevant.

As compared with the already marketed tablet formulation, exposures of IVA were unchanged when administered as the FDC granules. TEZ AUC was unchanged, while TEZ Cmax was approximately 13% lower following administration of the FDC granules relative to the reference FDC tablet, but the respective 90% CI fell within the pre-specified bounds of 0.7 and 1.43; therefore, the difference was deemed not clinically relevant.

Dose proportionality and time dependencies

The dose proportionality of ELX/TEZ/IVA exposure between ELX 100-mg/TEZ 50-mg/ IVA 75-mg and ELX 80-mg/TEZ 40-mg/IVA 60-mg FDC granules is expected based on the same formulation compositions and PK linearity of all 3 active substances. Indeed, linear pharmacokinetics of ELX/TEZ/IVA has been demonstrated within applied dose range.

Concomitant use with strong and moderate CYP3A inhibitors

Exposures of ELX, M23-ELX, TEZ, M1-TEZ, and IVA in CF patients aged 2 through 5 years of age receiving moderate or strong CYP3A inhibitors with the proposed dose modifications are similar to exposures in children aged 2 through 5 years of age or adults not receiving any CYP3A inhibitors, except from the

exposure of M1-TEZ in children receiving strong CYP3A inhibitors with the proposed dose adjustment in both weight groups. These exposures, which are approximately 2-fold lower than the 5th percentile of the exposure range for adults, still fall within the range of prior clinical experience. Newly submitted data, shows that the exposure between children aged 2-5 years old, and adults seems to be similar.

2.6.2.2. Pharmacodynamics

There are no new pharmacodynamic studies submitted.

Mechanism of action

Kaftrio is a triple combination product which contains the CFTR modulators elexacaftor (VX-445), ivacaftor and tezacaftor.

Tezacaftor and elexacaftor are correctors that facilitates the cellular processing and trafficking of CFTR to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor, as a CFTR potentiator that enhances the channel gating activity of the CFTR that is delivered to the cell surface.

Primary and Secondary pharmacology

No dedicated primary or secondary pharmacology studies in children 2 through 5 years of age are submitted which is acceptable by CHMP.

2.6.3. Discussion on clinical pharmacology

As compared with the already marketed tablet formulation, exposures of IVA were unchanged when administered as the FDC granules. TEZ AUC was unchanged, while TEZ Cmax was approximately 13% lower following administration of the FDC granules relative to the reference FDC tablet, but the respective 90% CI fell within the pre-specified bounds of 0.7 and 1.43; therefore, the difference was deemed not clinically relevant. The applicant assumed a coefficient of variation of 35%, based on which 90% CI were widened to 0.7 and 1.4. This is not entirely in line with the bioequivalence guideline.

However, the MAH has clarified that the granules formulation is not intended for the older age group, ie. >6 years old; therefore, the interchangeability issue is considered not relevant. In this respect, the CHMP agreed that there is no need to pursue further the question of meeting bioequivalence criteria or widening the acceptance range. However, the CHMP considered that exploring further the possibility of making the granules available to other age groups could be beneficial in future. Information that the formulations are not interchangeable has been introduced in section 5.2 of the SmPC.

A popPK modelling approach was used to describe the exposures of the three drugs in children aged 2-5 years due to sparse blood sampling performed in study 111.

The simulations results demonstrated that under the studied dosing regimen with a 14 kg weight cutoff, the exposures were within the 5th to 95th percentile of the observed exposure range for subjects ≥18 years of age for both weight groups.

M23-ELX exposures in some subjects 2 through 5 years of age who weighed ≥14 kg, were outside the 5th to 95th percentile of the observed exposure range for subjects ≥18 years of age from Studies 102 and 103; however, these exposures are within the adult exposure range previously shown to be safe and efficacious.

The majority of TEZ exposures were within the 5th and 95th percentile of the observed exposure range for subjects ≥18 years of age for each weight group. The range of M1-TEZ exposures for subjects 2 through 5

years of age is also generally below the maximum steady-state AUC observed from previous clinical studies of ELX/TEZ/IVA (Studies 102, 103, 104, and 106).

Overall, it can be concluded that in subjects 2 through 5 years of age, the majority of ELX, TEZ, and IVA exposures were within the exposure range observed for subjects ≥18 years of age for each weight group.

After administration of the FDC granules, exposures of ELX and TEZ were slightly lower relative to the reference FDC tablet, and exposures of IVA were unchanged in terms of AUC0-∞ and Cmax. The corresponding table in the SmPC was updated accordingly.

Co-administration with moderate or strong CYP3A4 inhibitors

The MAH was asked to report the simulated exposures to ELX, TEZ, and IVA with the proposed dose reduction for concomitant use with strong and moderate CYP 3A4 inhibitors in children aged 2-5 years. The provided simulations show that exposures of ELX, M23-ELX, TEZ, M1-TEZ, and IVA in CF patients aged 2 through 5 years of age receiving moderate or strong CYP3A inhibitors with the proposed dose modifications is similar to exposures in children aged 2 through 5 years of age or adults not receiving any CYP3A inhibitors, except from the exposure of M1-TEZ in children receiving strong CYP3A inhibitors with the proposed dose adjustment in both weight groups. These exposures, which are approximately 2-fold lower than the 5th percentile of the exposure range for adults, still fall within the range of prior clinical experience. Newly submitted data, as requested by CHMP, showed that the exposure between children aged 2-5 years old, and adults seems to be similar.

Patients with hepatic impairment

CF-related liver disease has been observed in patients with CF as young as 2 years of age. Although moderate and severe hepatic impairment is relatively rare in patients 2 through 5 years of age with CF, liver disease of this severity was seen in a prospective study. The proposed dose regimen for CF patients 2 through 5 years of age with hepatic impairment is based on the same approach used for older subjects.

Variability of the steady-state AUC for ELX, M23-ELX, TEZ, M1-TEZ, and IVA in subjects 2 through 5 years of age is similar to or lower than the variability observed in subjects 6 years of age and older. In addition, based on the provided simulations, the exposure to ELX, M23-ELX, TEZ is similar between subjects with moderate hepatic impairment, with the proposed dose reduction, and between subjects with normal hepatic function. Exposure to M1-TEZ and IVA is slightly lower with the proposed dose regimen in subjects with moderate hepatic function as compared to subjects without hepatic impairment, however, it is still within the 5th to 95th percentile of the observed exposure range for subjects ≥18 years of age for both weight groups.

Treatment of patients aged 2 to less than 6 years with moderate hepatic impairment (Child-Pugh Class B) is not recommended. For patients aged 2 to less than 6 years with moderate hepatic impairment, the use of Kaftrio should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose.

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, patients with severe hepatic impairment should not be treated with Kaftrio.

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A).

Dosing recommendations

For patients 2 through 5 years of age, ELX/TEZ/IVA is proposed to be administered with fat-containing food as follows (consistent with the dosing regimen evaluated in Study 111 Part B):

- Patients weighing ≥14 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h (i.e. there is an evening dose of 75 mg of Kalydeco granules)
- Patients weighing <14 kg: ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg qAM and 59.5 mg qPM (i.e. there is an evening dose of 59.5 mg of Kalydeco granules)

The proposed dosing recommendations were not in line with the dosing recommendations used in the clinical study, as in the clinical study, patients were included with weight ≥ 10 kg, therefore the safety in children with a weight < 10 kg is unknown.

The lowest weight CF patients 2 through 5 years of age were expected to be approximately 9 kg[3][4] by the MAH. Exposures in patients of this weight are expected to be similar to CF patients weighing 10 to 14 kg (who were considered in the popPK modeling). Therefore, no minimum weight is specified in the proposed dose regimen.

Using an approach similar to that used to select the dosing regimen for subjects 6 through 11 years of age, popPK analyses describing the data from Study 111 demonstrated that this proposed dose regimen resulted in exposures of ELX, TEZ, and IVA in subjects 2 through 5 years of age that are within the range of exposures that achieved efficacy in subjects ≥18 years of age. The simulation results also demonstrated that the exposures of metabolites M23-ELX and M1-TEZ with the proposed dosing regimens are generally within the range of exposures in previous clinical studies of ELX/TEZ/IVA and TEZ/IVA . Additional simulations showed that this proposed dosing regimen is optimal for patients 2 through 5 years of age. Exposure to M1-TEZ in children aged 2-5 years receiving strong CYP3A inhibitors with the proposed dose adjustment in both weight groups is approximately 2-fold lower than the 5th percentile of the exposure range for adults. Newly submitted data, as requested by CHMP, showed that the exposure between children aged 2-5 years old, and adults seems to be similar.

Although US CF Foundation (CFF) Patient Registry data indicates that only a small minority of children 2 through 5 years of age will have a weight < 10 kg, it is uncertain whether it also applies to the European population. Based on the 2021 Annual Report of the European Cystic Fibrosis Society Patient Registry (ECFSPR) it can be assumed that there are underweight children in the range from 2 to 5 years weighing less than 10 kg. Simulations were needed to anticipate whether adjusted dosing recommendations may be needed for children weighing 7 kg. simulations were requested to anticipate whether adjusted dosing recommendations may be needed for children with lower body weight. An increase for all analytes is observed, expected to be approximately 30% greater (with M1-TEZ being approximately 35% greater) for subjects weighing 7 kg than the simulated exposures for children weighing 10 kg. Therefore, a lower weight limit of 10 kg is proposed in the dosing recommendations for patients aged 2 to less than 6 years. This was adequately implemented by the MAH in section 4.2 of the SmPC.

[3] Centers for Disease Control and Prevention. CDC growth charts: percentile data files with LMS values. Available at: https://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed 21 March 2022.
[4] World Health Organization. Global database on child growth and malnutrition Available at: https://www.who.int/tools/child-growth-standards. Accessed 10 June 2022.

2.6.4. Conclusions on clinical pharmacology

In subjects 2 through 5 years of age, the majority of ELX, TEZ, and IVA exposures were within the exposure range observed for subjects ≥18 years of age for each weight group.

After administration of the FDC granules, exposures of ELX and TEZ were slightly lower relative to the reference FDC tablet, and exposures of IVA were unchanged in terms of AUC0-∞ and Cmax.

The granules are only to be indicated for children up to 5 years of age. Unfortunately, the applicant is not willing to further explore the possibility of making the granules available to other age groups.

Exposure to M1-TEZ in children aged 2-5 years receiving strong CYP3A inhibitors with the proposed dose adjustment in both weight groups is approximately 2-fold lower than the 5th percentile of the exposure range for adults. Newly submitted data, as requested by CHMP, showed that the exposure between children aged 2-5 years old, and adults seems to be similar.

An increase for all analytes is observed, expected to be approximately 30% greater (with M1-TEZ being approximately 35% greater) for subjects weighing 7 kg than the simulated exposures for children weighing 10 kg. Therefore, a lower weight limit of 10 kg is proposed in the dosing recommendations for patients aged 2 to less than 6 years. This was adequately implemented by the MAH in section 4.2 of the SmPC.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No specific dose response study was submitted.

2.6.5.2. Main study

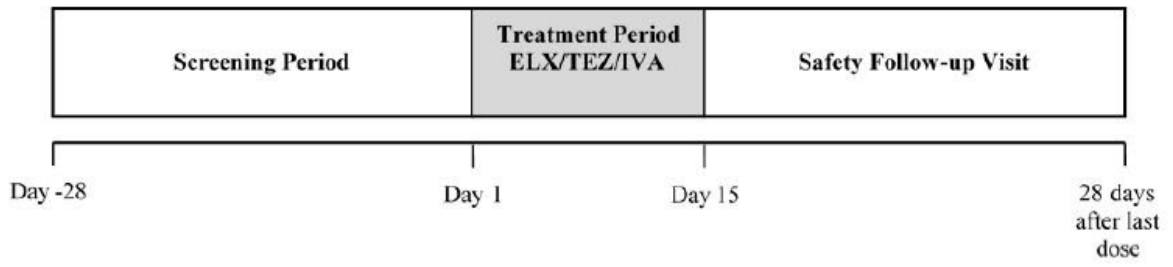
Study 111 Phase 3 Study Evaluating the Safety, Tolerability and Pharmacokinetics of Elexacaftor /Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age.

Methods

Study 111 Part A Design

Figure 2 shows the study design of part A. Subjects (F/F or F/MF genotypes) were planned for enrolment. A review of safety, tolerability, and available PK data was completed by an internal Vertex team after Part A to confirm the doses for Part B.

Figure 2: Part A Study Design



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

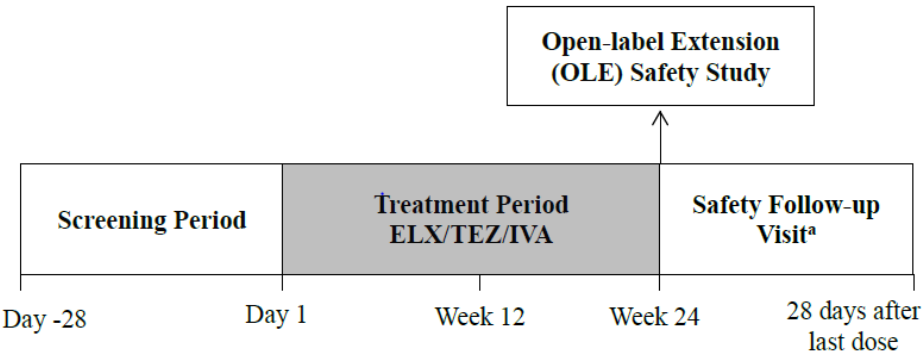
Study 111 Part B Design

Part B evaluated weight-based ELX/TEZ/IVA dosing for 24 weeks as shown in Figure 3.

Approximately 70 subjects, of which at least 30 subjects had F/MF genotypes and at least 15 subjects had the F/F genotype were planned for enrolment. At least 25 subjects were between 2 and 3 years of age (inclusive).

Subjects who completed the Part B Treatment Period and did not permanently discontinue study drug could enrol in an optional open-label extension (OLE) safety study.

Figure 3: Study 111 Part B Study Design



ELX: elexacaftor; IVA: ivacaftor; OLE: open-label extension; TEZ: tezacaftor
[a] The Safety Follow-up Visit was not required for subjects who enrolled in an OLE safety study within 28 days of the last scheduled visit in the Treatment Period.

Study Participants

A total of 75 subjects enrolled and were administered ELX/TEZ/IVA for up to 24 weeks, which was chosen to provide an adequate assessment of safety. Approximately 70 subjects, of which at least 30 subjects had F/MF genotypes and at least 15 subjects had the F/F genotype, were planned for enrolment. At least 25 subjects were between 2 and 3 years of age (inclusive).

Subjects were enrolled at 22 sites in North America, Europe, and Australia.

Subjects who completed the Part B Treatment Period and did not permanently discontinue study drug could enrol in an optional open-label extension (OLE) safety study (enrolment was based on the eligibility criteria specified within the OLE safety study protocol).

Inclusion criteria

1. Subject's legally appointed and authorized representative signed and dated an informed consent form (ICF).

2. Subjects (males and females), 2 through 5 years of age, inclusive, on the date of informed consent (and assent, as applicable).

3. In Part A subjects who weighed ≥14 kg at Day1. In Part B subjects who weighed ≥10 kg at the Screening Visit.

4. Confirmed diagnosis of CF as determined by the investigator.

5. In Part A, subjects who are homozygous for F508del (F/F genotype) or heterozygous for F508del and an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotypes). In Part B, subjects who have at least 1 F508del mutation in the CFTR gene or an ELX/TEZ/IVA-responsive CFTR mutation.

- Genotype was confirmed at the Screening Visit. This assessment did not need to be repeated for confirmed subjects in Part A who wished to participate in Part B.
- If the screening CFTR genotype result was not received before the first dose of study drug, a previous CFTR genotype laboratory report could be used to establish eligibility.
- Subjects who were enrolled and whose screening genotype did not confirm study eligibility were discontinued from the study.

6. Subjects with stable CF disease at the start of the Treatment Period as deemed by the investigator.

7. Subjects who were willing to remain on a stable CF medication regimen (other than CFTR modulators) through Day 15 (Part A) or through Week 24 (Part B) or, if applicable, through the Safety Follow-up Visit.

8. As judged by the investigator, the parent or legal guardian was able to understand protocol requirements, restrictions, and instructions and the parent or legal guardian was able to ensure that the subject would comply with and was likely to complete the study as planned.

Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might have confounded the results of the study or pose an additional risk in administering study drug(s) to the subject. This included, but was not limited to, the following:

- Clinically significant cirrhosis with or without portal hypertension
- Solid organ or haematological transplantation
- Cancer

2. Any clinically significant laboratory abnormalities at the Screening Visit that would have interfered with the study assessments or posed an undue risk for the subject (as deemed by the investigator).

3. Any of the following abnormal laboratory values at screening:

- Haemoglobin <10 g/dL
- Total bilirubin, aspartate transaminase (AST), or alanine transaminase (ALT) ≥2 × upper limit of normal (ULN)
- Alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) ≥3 × ULN
- Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)

4. An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).

5. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus). For subjects who had a history of a positive culture, the investigator applied the following criteria to establish whether the subject was free of infection with such organisms:

- The subject did not have a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
- The subject had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.

6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).

7. Ongoing or prior participation in an investigational drug study (including studies investigating ELX with or without coadministration with other study drugs) within 28 days of the Screening Visit.

- A washout period of 5 terminal half-lives of the previous investigational study drug, or 28 days, whichever was longer, elapsed before the Screening Visit.
- The duration of the elapsed time may have been longer if required by local regulations.

  Note: Ongoing participation in a noninterventional study (including observational studies) was permitted.

8. Use of restricted medication within specified duration before the first dose of study drug as defined in protocol.

9. The subject or a close relative of the subject was the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

10. Part B only: Elevated serum ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN in the previous year.

Treatments

Investigational Drug

Table 4: Parts A and B Doses

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
≥14 kg only	100 mg qd	50 mg qd	75 mg q12h
Part B			
≥14 kg	100 mg qd	50 mg qd	75 mg q12h
≥10 kg to <14 kg	80 mg qd	40 mg qd	60 mg qAM 59.5 mg qPM

ELX: elexacaftor; IVA: ivacaftor; qAM: once every morning; qd: once daily; qPM: once every evening; q12h: every 12 hours; TEZ: tezacaftor

Prohibited Medications

Table 5: Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, are prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drugs	None allowed within 28 days before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

CYP: cytochrome P450; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

[a] Ciprofloxacin is not a moderate CYP3A inhibitor on the basis of results of a drug-drug interaction study conducted with IVA, a sensitive CYP3A substrate (Kalydeco [ivacaftor] US Package Insert).

Prior and concomitant medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected from each subject's source documentation for medications taken within 56 days before the Screening Visit through completion of study participation.

For subjects who are screened but are not subsequently enrolled, details of prior medication will be documented only in the subject's source documents.

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day 1 Visit through completion of study participation. A stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:
    - Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
    - Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of the study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle of the inhaled antibiotic.
    - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of the study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.

- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically or up to 60 mg daily for up to 5 days.
- Subjects who are using a bronchodilator should have their Multiple-breath Washout (MBW) assessments performed according to the guidelines provided in the protocol, Section 11.4.2.

Dose Modification for Toxicity

Modifications of the study drug dose were prohibited. Should any unacceptable toxicity arise, individual subjects were withdrawn from the study, and dosing ceased.

Drug Interruption and Stopping Rules

In subjects who interrupted the study drug for >72 hours for any reason, the investigator resumed study drug only after a thorough investigation of the cause for the interruption.

Liver Function Tests

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, with or without total bilirubin >2 × ULN, must be followed closely, including confirmatory testing performed by the central laboratory within 48 to 72 hours and subsequent close monitoring of ALT, AST, and bilirubin levels, as clinically indicated. If a subject cannot return to the site for confirmatory testing, a local laboratory may be used.

Study drug administration must be interrupted immediately (prior to confirmatory testing) if any of the following criteria are met:

• ALT or AST >8 × ULN

• ALT or AST >5 × ULN for more than 2 weeks

• ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice

Study drug administration must be discontinued if the following criteria are met:

• Subsequent ALT or AST values confirm the initial elevation that satisfied the interruption rule (above), and no convincing alternative aetiology is identified, regardless of whether transaminase levels have improved.

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases return to baseline or are ≤ 2 x ULN, whichever is higher. Upon resumption of the study drug, transaminases and bilirubin should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation interruption threshold recurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed aetiology.

Rash

Study drug dosing should be interrupted if a subject develops a generalized rash of Grade 3 or higher, or a rash that is considered a serious adverse event (SAE). The investigator may consider resumption of study drug if considered clinically appropriate.

Objectives

The study objectives are described in Table 6 below.

Table 6: Study Objectives

Part A	Part B
Treatment duration: 15 days	Treatment duration: 24 weeks
Objectives: *Primary:* • PK of ELX, TEZ, and IVA • Safety and tolerability of ELX/TEZ/IVA *Secondary:* None	**Objectives:** *Primary:* • Safety and tolerability of ELX/TEZ/IVA *Secondary:* • PK of ELX/TEZ/IVA • PD of ELX/TEZ/IVA • Efficacy of ELX/TEZ/IVA

ELX: elexacaftor; IVA: ivacaftor; PD: pharmacodynamics; PK: pharmacokinetics; TEZ: tezacaftor.

Outcomes/endpoints

PK assessment

Parts A and B

Blood samples collected to determine PK parameters for ELX, M23-ELX, TEZ, M1-TEZ, IVA, and M1-IVA.

PD and Efficacy Assessments

Part B

Sweat chloride (SwCl), multiple-breath washout (MBW; subjects ⩾3 years of age at screening of Part B), weight, height, and other events related to outcome (e.g., pulmonary exacerbations [PEx])

Safety Assessments

Parts A and B

Adverse events (AEs), clinical laboratory assessments (serum chemistry, haematology, coagulation, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations, and physical examinations (PEs)

Other Assessments

Part B

- Faecal samples for faecal elastase-1 (FE-1) and calprotectin to assess exocrine pancreatic function and gastrointestinal inflammation, respectively.
- Blood samples for immunoreactive trypsinogen (IRT) to assess exocrine pancreatic function.
- Modified Facial Hedonic Scale to assess drug acceptability and palatability.

Sample size

Part A

Approximately 14 subjects were planned to be enrolled in Part A. Sample size calculations were determined based on ELX and M23-445 estimates of clearance. Assuming that the variability in this age group was the same as the variability observed in adults, data from 14 subjects would allow at least 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-445.

Part B

A total of 75 subjects enrolled and were administered ELX/TEZ/IVA for up to 24 weeks, which was chosen to provide an adequate assessment of safety.

No formal power calculation was performed.

Assuming a dropout rate of 10% or 20%, approximately 63 or 56 subjects, respectively, were expected to complete Part B.

Randomisation and blinding (masking)

This was an open-label study. Randomization was not required because all subjects were treated identically. An interactive web response system was used to dispense dosage based on subject weight.

Subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) were not informed of their study-related LCI, sweat chloride (SwCl), faecal elastase-1 (FE-1), calprotectin, and immunoreactive trypsinogen (IRT) results during the Treatment Period (Part B only), regardless of whether the subject permanently discontinued treatment.

Statistical methods

Analyses Sets

The following analysis sets were defined separately for Part A and Part B.

The All Subjects Set included all subjects who were enrolled (defined as subjects having data in the clinical database for this study) or received at least 1 dose of study drug. This analysis set was used for all individual subject data listings and disposition summary tables, unless otherwise specified.

The Safety Set included all subjects who received at least 1 dose of study drug. The Safety Set was used for all safety analyses.

The Full Analysis Set (FAS) included all subjects who were enrolled and carry the intended CFTR allele mutation and received at least 1 dose of study drug. The FAS was used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy and PD endpoints, unless otherwise specified.

Analyses methods

Analysis methods for PD and efficacy endpoints are summarized in Table 7. All P values are considered nominal.

Table 7: Study 111 Part B PD and Efficacy Endpoints and Methods

Endpoint	Method of Analysis Analysis Details
Secondary PD and Efficacy Endpoints	

Absolute change in SwCl from baseline through Week 24	• MMRM
	  • Based on FAS
	  • Change from baseline in SwCl as dependent variable, visit as fixed effect, and baseline SwCl and genotype group (F/F vs. F/MF) as covariates
	  • Estimated using restricted maximum likelihood
	  • Degrees of freedom estimated using Kenward-Roger approximation
	  • Unstructured covariance used to estimate within-subject errors
	  • Missing data were not imputed
	• LS mean (95% CI) and *P* value through Week 24
	• Line plot
	• Subgroup analysis by genotype group (F/F or F/MF)[a]

Absolute change in $LCI_{2.5}$ from baseline through Week 24	• MMRM
	  • Based on subjects in FAS with at least one MBW assessment
	  • MMRM similar to SwCl with baseline $LCI_{2.5}$ as covariate instead of SwCl
	• LS mean (95% CI) and *P* value through Week 24
	• Line plot
	• Ad hoc subgroup analysis by genotype group (F/F or F/MF)[a]

Other Efficacy Endpoints	
Number of PEx and CF-related hospitalizations through Week 24	• Descriptive statistics (annualized event rate)
Absolute change in weight and weight-for-age z-score from baseline at Week 24	• MMRM • LS mean (95% CI) at Week 24 • Line plot
Absolute change in height and height-for-age z-score from baseline at Week 24	• MMRM • LS mean (95% CI) at Week 24 • Line plot
Absolute change in BMI and BMI-for-age z-score from baseline at Week 24	• MMRM • LS mean (95% CI) at Week 24 • Line plot
Absolute change in FE-1 levels from baseline at Week 24	• Descriptive statistics • Shift from baseline analysis
Absolute change in fecal calprotectin levels from baseline at Week 24	• Descriptive statistics
Absolute change in serum levels of IRT from baseline at Week 24	• Descriptive statistics
Drug acceptability and palatability assessment using Modified Facial Hedonic Scale	• Descriptive statistics (by category)

BMI: body mass index; CF: cystic fibrosis; FAS: Full Analysis Set; FE-1: fecal elastase-1; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IRT: immunoreactive trypsinogen; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MBW: multiple-breath washout; MMRM: mixed-effects model for repeated measures; PD: pharmacodynamic; PEx: pulmonary exacerbation; SwCl: sweat chloride

[a] Only subjects with F/F and F/MF genotypes enrolled in Study 111 Part B (Section 4.2.1) therefore subgroup analyses were based on these 2 groups.

The MMRM was used to estimate the within-group mean absolute change in SwCl through Week 24. The model included absolute change from baseline in SwCl (including all measurements up to and including Week 24) as the dependent variable and visit as the fixed effect, with baseline SwCl value and genotype group (F/F vs F/MF) as covariates. The model was estimated using restricted maximum likelihood. Denominator degrees of freedom for the F-test of fixed effects were estimated using the Kenward-Roger approximation. An unstructured covariance structure was used to model the within-subject errors. If the model estimation did not converge, a compound symmetry covariance structure was used instead. Conditional on the observed data and covariates, missing data were assumed to be missing at random; consequently, no imputation of missing data was performed.

The statistical analysis plan (SAP) was developed and finalized before the database lock.

Sensitivity Analysis

Not applicable because the primary endpoints were safety and tolerability assessments.

Subgroup Analysis

The absolute change in SwCl from baseline through Week 24 was analysed for the subgroup according to genotype group (F/F, F/MF).

The same MMRM model was conducted for each subgroup, with the genotype group removed from covariates.

Results

Participant flow

Part A

A total of 18 subjects were enrolled in Part A. No subjects discontinued treatment or withdrew from the study.

Part B

The efficacy analyses in Part B were based on the FAS, which included 75 subjects. Overall, 74 (98.7%) subjects completed treatment and the study. One (1.3%) subject discontinued due to an AE.

Recruitment

Part A

Subjects were enrolled at 7 sites in the United States.

Study initiation: 19 November 2020 (date the first eligible subject signed the informed consent form)

Study completion: 05 March 2021 (date the last subject completed the last visit)

Part B

Subjects were enrolled at 22 sites in North America, Europe, and Australia.

Study initiation: 19 July 2021 (the date the first eligible subject signed the informed consent form).

Study completion: 03 June 2022 (the date the last subject completed the last visit).

Conduct of the study

The global study protocol was amended twice; country-specific amendments were prepared for 1 country.

Protocol amendments

The original study protocol dated 19 June 2020 was amended twice (Jun 2021 and Oct 2021). Changes mostly pertained clarifications and updates in definitions or measurements, i.e. ophthalmologic examinations were removed as part of the safety endpoint. Furthermore, the study population in Part B was expanded to include subjects who have at least 1 F508del mutation in the CFTR gene or an ELX/TEZ/IVA-responsive CFTR mutation.

Country-specific amendments were prepared for 1 country.

The Statistical Analysis Plan (SAP) was amended once to create the SAP Version 2.0, dated 02 May 2022 to incorporated updates in Clinical Study Protocol (CSP) Version 3.0 and added planned analysis for Part B.

Important protocol deviation (IPD)

An important protocol deviation (IPD) was defined as any protocol deviation that may have significantly affected the completeness, accuracy, or reliability of the study data or that may have significantly affected a subject's rights, safety, or well-being.

Part A

One subject had an IPD in Part A related to eligibility criteria. The screening haemoglobin sample was haemolyzed upon receipt at the laboratory and was inadvertently not redrawn; therefore, exclusion criterion 3 (haemoglobin <10 g/dL) could not be determined. Day 1 pre-dose laboratory results showed that haemoglobin was >10 g/dL.

Part B

No subjects had IPDs in Part B

Baseline data

Part B

The mean population age was 4.1 years, and over half (54.7%) of the subjects were female. The majority of subjects (90.7%) were White, and 8.0% were Hispanic or Latino. A total of 23 (30.7%) subjects had an F/F genotype, 52 (69.3%) subjects had F/MF genotypes (with 30 distinct F/MF genotypes represented), and no subjects had other ELX/TEZ/IVA-responsive genotypes. At baseline, the mean SwCl was 100.7 mmol/L and the mean LCI2.5 was 8.41. The most common concomitant medications were those typically used for the management of CF.

Table 8: Subject Demographics (FAS, Part B)

Demographic	ELX/TEZ/IVA N = 75
Sex, n (%)	
Male	34 (45.3)
Female	41 (54.7)
Age group at screening, n (%)	
≥2 to <3 years	11 (14.7)
≥3 to <4 years	27 (36.0)
≥4 to <5 years	22 (29.3)
≥5 to <6 years	15 (20.0)
Age at baseline (years)	
n	75
Mean (SD)	4.1 (1.1)
Median	4.0
Min, max	2.1, 6.0
Ethnicity, n (%)	
Hispanic or Latino	6 (8.0)
Not Hispanic or Latino	63 (84.0)
Not collected per local regulations	6 (8.0)
Race, n (%)	
White	68 (90.7)
Black or African American	2 (2.7)
Not collected per local regulations	6 (8.0)
Geographic region, n (%)	
North America	52 (69.3)
Europe and Australia	23 (30.7)

Source: Table 14.1.3.1b
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; N: total sample size; n: size of subsample; TEZ: tezacaftor
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. If a subject was reported to have multiple races, then the subject was counted for each race reported.

Table 9: Baseline Characteristics (FAS, Part B)

Characteristic	ELX/TEZ/IVA N = 75
CFTR genotype group, n (%)	
F/F	23 (30.7)
F/MF[a]	52 (69.3)
Other	0
Weight group, n (%)	
<14 kg	16 (21.3)
≥14 kg	59 (78.7)

Weight (kg)	
n	75
Mean (SD)	16.5 (3.2)
Median	16.3
Min, max	10.8, 26.0
Weight z-score[b]	
n	75
Mean (SD)	-0.07 (0.89)
Median	-0.03
Min, max	-2.62, 2.23
Height (cm)	
n	75
Mean (SD)	101.8 (9.2)
Median	100.7
Min, max	83.9, 125.5
Height z-score[b]	
n	75
Mean (SD)	-0.09 (1.10)
Median	-0.22
Min, max	-3.11, 3.58
BMI (kg/m^2)[c]	
n	75
Mean (SD)	15.79 (1.06)
Median	15.67
Min, max	13.70, 18.56
BMI z-score[b]	
n	75
Mean (SD)	0.09 (0.85)
Median	0.17
Min, max	-1.98, 1.59
Sweat chloride (mmol/L) at baseline	
n	71
Mean (SD)	100.7 (11.2)
Median	104.0
Min, max	58.0, 115.0
$LCI_{2.5}$ at baseline[d]	
n	51
Mean (SD)	8.41 (1.48)
Median	7.93
Min, max	6.75, 12.47
Prior use of CFTR modulator, n (%)[e]	
Yes	10 (13.3)
No	65 (86.7)

Prior use of dornase alfa, n (%)[e]	
Yes	33 (44.0)
No	42 (56.0)
Prior use of azithromycin, n (%)[e]	
Yes	8 (10.7)
No	67 (89.3)
Prior use of inhaled antibiotic, n (%)[e]	
Yes	8 (10.7)
No	67 (89.3)
Prior use of any bronchodilator, n (%)[e]	
Yes	51 (68.0)
No	24 (32.0)
Prior use of any inhaled bronchodilator, n (%)[e]	
Yes	51 (68.0)
No	24 (32.0)
Prior use of any inhaled hypertonic saline, n (%)[e]	
Yes	37 (49.3)
No	38 (50.7)
Infection with *Pseudomonas aeruginosa* within 2 years prior to screening, n (%)	
Positive	14 (18.7)
Negative	61 (81.3)

Source: Table 14.1.4.1b

BMI: body mass index; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to $1/40^{th}$ of its starting value: MBW: multiple-breath washout; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B.

[a] One subject had an *F508del* mutation on the first allele, and a second mutation that was considered both MF and ELX/TEZ/IVA-responsive (*I502T*) on the second allele. For analysis purposes, this subject was considered F/MF.

[b] Z-scores were calculated using National Center for Health Statistics growth charts.

[c] BMI = weight / (height × height) (kg/m^2).

[d] For subjects in the FAS who had performed MBW as an assessment at least once.

[e] Includes medications administered during the 56 days before the first dose of study drug in Part B.

Numbers analysed

All sets, i.e. All Subjects Set, FAS and Safety Set, included 75 subjects (100%).

No major compliance issues were identified in Parts A or B.

Outcomes and estimation

Secondary Endpoints

Sweat chloride

Treatment with ELX/TEZ/IVA resulted in an improvement (reduction) in SwCl as estimated by the within-group least squares (LS) mean absolute change from baseline through Week 24: -57.9 mmol/L (95% CI: -61.3, -54.6; nominal P<0.0001).

Table 10: MMRM Analysis of Absolute Change From Baseline in SwCl Through Week 24 (FAS, Part B)

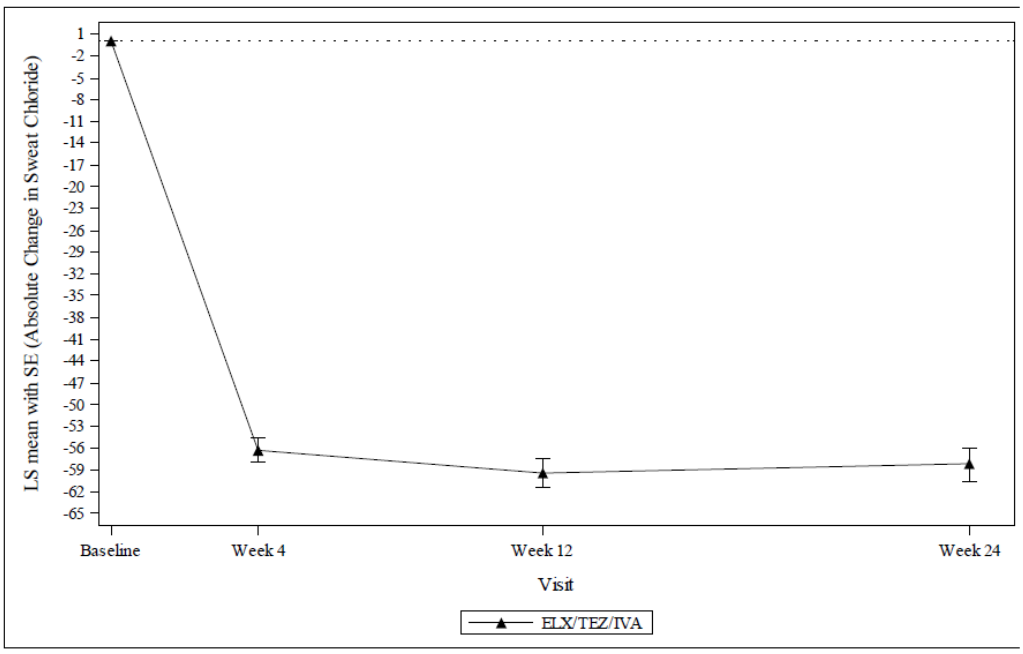
	ELX/TEZ/IVA N = 75
Baseline	
n	71
Mean (SD)	100.7 (11.2)
Absolute change through Week 24	
n	69
LS mean (SE)	-57.9 (1.7)
95% CI of LS mean	(-61.3, -54.6)
P value	<0.0001

Source: Table 14.2.1.2b

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24 in Part B, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Figure 4: MMRM Analysis of Absolute Change From Baseline in SwCl (mmol/L) by Visit (FAS, Part B)



Source: Figure 14.2.1b

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24 in Part B, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Lung Clearance Index 2.5

Treatment with ELX/TEZ/IVA resulted in an improvement (reduction) in $LCI_{2.5}$ in subjects with MBW assessments as estimated by the within-group LS mean absolute change from baseline through Week 24: -0.83 (95% CI: -1.01, -0.66; nominal P<0.0001).

Table 11: MMRM Analysis of Absolute Change From Baseline in LCI2.5Through Week 24 (FAS For Subjects With MBW Assessments, Part B)

	ELX/TEZ/IVA N = 63
Baseline	
n	51
Mean (SD)	8.41 (1.48)
Absolute change through Week 24	
n	50
LS mean (SE)	-0.83 (0.09)
95% CI of LS mean	(-1.01, -0.66)
P value	<0.0001

Source: Table 14.2.2.2b

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MBW: multiple-breath washout; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24, with visit as fixed effect and baseline $LCI_{2.5}$ and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. The analysis was based on subjects in the FAS who had performed MBW as an assessment at least once.

Other Endpoints

Exacerbations

Through Week 24 of ELX/TEZ/IVA treatment, 12 (16.0%) subjects had PEx events. The annualized event rate was 0.32 events/year for PEx (12 events). One subject (1.3%) had a PEX requiring hospitalization. The annualized event rate was 0.03 event/year (1 event) . One subject (1.3%) had a PEX requiring antibiotic therapy. The annualized event rate was 0.03 event/year (1 event).

Growth parameters

LS mean absolute changes from baseline at Week 24 for growth parameters were:

- Weight: 1.0 kg (95% CI: 0.9, 1.2)
- Weight z-score: 0.02 (95% CI: -0.04, 0.09)
- Height: 3.1 cm (95% CI: 2.8, 3.3)
- Height z-score: -0.06 (95% CI: -0.11, 0.00)
- BMI: 0.03 kg/m2 (95% CI: -0.10, 0.17)
- BMI z-score: 0.10 (95% CI: 0.00, 0.20)

Markers of pancreatic function and inflammation

Pancreatic function: At baseline, the mean (SD) FE-1 level was 28.1 (65.7) mg/kg, and the mean (SD) change from baseline at Week 24 was 39.5 (89.2) mg/kg. Two (2.7%) subjects had baseline FE-1 levels ⩾ 200 mg/kg, and FE-1 levels remained ⩾200 mg/kg at Week 24 for both subjects. Four (5.3%) subjects had baseline FE-1 levels <200 mg/kg and FE-1 levels ⩾200 mg/kg at Week 24.

Pancreatic inflammation: At baseline, the mean (SD) serum IRT level was 266.3 (345.1) µg/L, and the mean (SD) change from baseline at Week 24 was -166.6 (285.0) µg/L.

Gastrointestinal inflammation: At baseline, the mean (SD) calprotectin level was 388.50 (659.45) mg/kg, and the mean (SD) change from baseline at Week 24 was -289.66 (719.72) mg/kg.

Drug acceptability/palatability assessment

In a drug acceptability/palatability assessment using the Modified Facial Hedonic Scale, when taking ELX/TEZ/IVA at Week 24, 28 (40.0%) subjects "liked it very much" and 11 (15.7%) subjects "liked it a little."

2.6.5.3. Ancillary analyses

A predefined subgroup analysis by genotype subgroup was performed for SwCl (Table 12) and LCI2.5 (Table 13). Results were generally similar for the F/F and F/MF subgroups.

Table 12: MMRM Analysis of Absolute Change From Baseline in SwCl (mmol/L) Through Week 24 by Genotype Group (FAS, Study 111 Part B)

Genotype Subgroup Statistic	ELX/TEZ/IVA N = 75
F/F genotype	
n	22
LS mean (SE)	-70.0 (2.6)
95% CI of LS mean	(-75.4, -64.5)
F/MF genotypes	
n	47
LS mean (SE)	-52.6 (2.1)
95% CI of LS mean	(-56.9, -48.4)

Source: Study 111 CSR/Table 14.2.1.4b

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline SwCl as covariate. A similar MMRM method as the analysis for SwCl was applied to each subgroup category. Model-based estimates for a given category were displayed provided the analysis converged in that category.

Table 13: MMRM Analysis of Absolute Change From Baseline in LCI2.5 Through Week 24 by Genotype Group (FAS, Study 111 Part B)

Genotype Subgroup Statistic	ELX/TEZ/IVA N = 63
F/F genotype	
n	17
LS mean (SE)	-0.89 (0.12)
95% CI of LS mean	(-1.15, -0.63)
F/MF genotypes	
n	33
LS mean (SE)	-0.82 (0.12)
95% CI of LS mean	(-1.06, -0.57)

Source: Study 111 CSR/Ad hoc Table 14.2.2.4b

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th (2.5%) of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size for subjects with MBW assessments in the FAS; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline $LCI_{2.5}$ as covariate. A similar MMRM method as the analysis for $LCI_{2.5}$ was applied to each subgroup category. Model-based estimates for a given category were displayed provided the analysis converged in that category.

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 14: Summary of efficacy for trial 111

Title: A Phase 3 Study Evaluating the Safety, Tolerability and Pharmacokinetics of Elexacaftor /Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age		
Study identifier	EudraCT Number: 2020-002251-38 Study VX20-445-111 Vertex Report Number: S120	
Design	Phase 3, open-label, multicenter study Part B	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks treatment period Not applicable As extension part, patients rolled in a separate study
Hypothesis	Exploratory: efficacy is a secondary objective, no formal hypothesis	

Treatments groups	Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)		Treatment < 14 kg and ≥10 kg: 80 mg ELX qd/40 mg TEZ qd/60 mg IVA qd AM and IVA 59.5 qd PM ⩾14 kg: 100 mg ELX qd/50 mg TEZ qd/75 mg IVA qd AM and IVA 75 qd PM Duration: 24 weeks Number: 75 in total
Endpoints and definitions	Secondary endpoint	Sweat chloride (SwCl)	Absolute change in SwCl from baseline through week 24
	Secondary endpoint	LCI2.5	Absolute change in LCI2.5 from baseline through week 24
	Exploratory endpoint	Pulmonary exacerbations	annualized event rate
Database lock	21 June 2022		

Results and Analysis

The primary analysis is the analysis of the changes from baseline.

Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Analysis Set (FAS): all subjects who are enrolled and carry the intended CFTR allele mutation and received at least 1 dose of study drug	
Descriptive statistics and estimate variability	Treatment group	ELX/TEZ/IVA
	Number of subject	75
	LS mean SwCl (SE)	-57.9 (1.7)
	95% CI of LS mean SwCl *p-value*	-61.3, -54.6 *<0.0001*
	LS mean LCI2.5 (SE)	-0.83 (0.09)
	95% CI of LS mean LCI2.5 *p-value*	-1.01, -0.66 *<0.0001*

	PEx rate	0.32

2.6.5.4. Clinical studies in special populations

N/A

2.6.5.5. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.7. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

The results of Study VX20-445-111 (Study 111) are submitted to support an extension of indication of ELX/TEZ/IVA to include CF patients 2 through 5 years of age. Study 111 is a phase 3, multicentre study conducted in 2 parts to evaluate the pharmacokinetics (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects 2 through 5 years of age who have at least one F508del mutation.

Principle of Extrapolation

The extension of the indication to children 2 through 5 years of age is based on the principle of partial extrapolation from adults and adolescents to paediatric patients and has been accepted for the extension of indication of Kaftrio to CF patients 6 through 11 years of age (EMEA/H/C//005269/X/0008) and Symkevi (TEZ/IVA) (EMEA/H/C/004682/X/0015).

Consistent with the principles described in ICH E-16, extrapolation of efficacy from adults to a younger population based on comparable PK exposures and safety is acceptable, because the disease process in CF patients of all age groups stems from a common aetiology of dysfunctional CFTR protein that is targeted by ELX/TEZ/IVA. The defect of the defective chloride channels is already present at birth. Because ELX/TEZ/IVA targets the dysfunctional CFTR, the outcome of therapy is expected to be comparable in younger age groups compared to adults to be shown with a similar reduction in the pharmacodynamic parameter sweat chloride.

Extrapolation of efficacy is also supported by previously demonstrated efficacy in controlled studies of CF subjects 6 through 11 years of age treated with other CFTR modulators (LUM/IVA and TEZ/IVA), which was comparable to the effect observed in adults.

This is also outlined in the EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) that describes the requirements of the application of the (partial) extrapolation, i.e., confirmation of the dose by PK study in children and bridging of safety and efficacy data in children.

Design and conduct of clinical studies

In part B, subjects were treated with ELX/TEZ/IVA for 24 weeks according to the following schedule:

- subjects <14 kg and ≥10 kg: ELX/TEZ/IVA 80 mg/40 mg/60 mg qAM granules and IVA 59.5 mg qPM granules

- subjects ≥14 kg: ELX/TEZ/IVA 100 mg qd/50 mg qd/75 mg q12h FDC granules and IVA 75 mg q12h granules

Subjects who completed the Part B Treatment Period and did not permanently discontinue the study drug could enrol in an optional open-label extension safety study (if they met the eligibility criteria for that study).

Similar modification, interruption and discontinuation rules and prohibited medication rules are applied as for the adults in the marketing application studies and are acceptable.

The study's primary objectives were to evaluate the pharmacokinetics (part A) and the safety and tolerability of ELX/TEZ/IVA through Week 24 (Part B). Efficacy was a secondary objective and was only measured in Part B.

Endpoints

As safety is the primary objective in Study 111 Part B, efficacy parameters were defined as secondary outcome measures. This approach is acceptable.

Sweat chloride, as a pharmacodynamic parameter, is an important parameter for measuring the effect of a modulator. In CF, sweat chloride is increased due to a defect in the CFTR modulator. This defect is assumed to be similar in the adult and paediatric populations. A decrease in SwCL can be considered as an effect on the underlying pathology.

Pulmonary function test, i.e. multiple breath wash-out (MBW) for calculating $LCI_{2.5}$ is considered important to measure an effect on the lungs, one of the most important affected organs in CF. The $LCI_{2.5}$ can measure changes in the small airways. In CF, the small airways are affected earlier than the large airways. Therefore, the use of the $LCI_{2.5}$ as a measurement of efficacy is sensitive, given the more preserved lung function in children than in adults. Changes in BMI z-score and height z-score inform over the nutritional status, while FE-1, faecal calprotectin and IRT inform over the pancreatic function. Thus all parameters inform about a different aspect of CF and are considered valuable.

The indication of Kaftrio is broad, including patients with severe CF and patients with less severe CF.

Statistics

As study 111 is an open-label single-arm trial without a comparator arm, no randomisation or blinding was done. Considering that acceptance of an extension of the indication could be based on similar exposure, safety, and efficacy as in adults and adolescents, a within-group change from baseline is considered acceptable to provide evidence of comparable efficacy with adults and adolescents.

Each continuous efficacy and PD endpoint was analysed using a mixed-effects model for repeated measures that included visit as the fixed effect, with a baseline value of the efficacy variable and genotype group (F/F or F/MF) as covariates. The model included all measurements of the efficacy variable up to Week 24 (inclusive).

Study 111 was in line with the paediatric investigational plan (PIP) as outlined in the positive compliance check.

Currently, the granules are only asked to be indicated for children up to 5 years of age, while an unmet need in children older than 5 years of age and adults who cannot use tablets may exist for a formulation other than tablets. The CHMP considers unfortunate that the MAH does not further explore the possibility of making the granules available to other age groups, as there might be a need for patients who have difficulties swallowing tablets because of a concomitant disorder.

Efficacy data and additional analyses

A total of 75 subjects were enrolled and received at least 1 dose of the study drug, and 74 (98.7%) subjects completed treatment and the study. One subject discontinued due to an AE.

The mean population age was 4.1 years, and over half (54.7%) of the subjects were female. The majority of subjects (90.7%) were White, and 8.0% were Hispanic or Latino. A total of 23 (30.7%) subjects had an F/F genotype, 52 (69.3%) subjects had F/MF genotypes, with 30 distinct F/MF genotypes represented, and no subjects had other ELX/TEZ/IVA-responsive genotypes. This population is considered representative of the intended population as established in the adult population.

Of the studied population, 86.7% of the subjects did not use a modulator before. For patients with a specific gating mutation, modulator therapy is currently authorised for this age group. Therefore , the studied populations consisted of modulator-experienced and modulator naïve subjects.

Outcomes and estimation

As this was an open-label, single-arm study, the outcomes of the efficacy parameters were results compared to baseline.

Treatment with ELX/TEZ/IVA resulted in the LS mean absolute change in SwCl from baseline through Week 24 of -57.9 mmol/L (95% CI: -61.3, -54.6; P<0.0001). The CHMP has accepted a reduction of -10 mol/L in SwCl as clinically relevant. Therefore, the reduction in SwCl can be considered clinically relevant. This reduction is comparable with results observed in children aged 6 through 11 years of age and in the adult and adolescent populations.

An improvement in ventilation inhomogeneity measured by $LCI_{2.5}$ is shown by a numerical decrease from baseline. The LS mean absolute change in LCI2.5 from baseline through Week 24 was -0.83 (95% CI: -1.01, -0.66; P<0.0001. The improvement (reduction) from baseline is smaller than the reduction observed in children 6-11 years (-1.71 (95% CI: -2.11, -1.30)). However, lung function in young children is better preserved than in children 6 through 11 years of age. Therefore, a slightly lower benefit is not unexpected. Of note, a minimal clinically important difference (MCID) for the $LCI_{2.5}$ is not established for this population. Therefore, an effect larger than the natural variability might be regarded as clinically relevant. The improvement in the $LCI_{2.5}$ over time will therefore indicate the efficacy of the drug in this young but still severely affected population. Results of the study have been reflected in section 5.1 of the SmPC.

Results of growth parameters were considered supportive of a benefit as they were stable or showed an improvement supporting the benefit of treatment. Also, markers of pancreatic function and inflammation were considered supportive as improvements in FE-1 level, Faecal calprotectin and serum IRT were observed.

Subgroup analyses for different patient groups showed that the results in SwCl were somewhat better in the F/F patients, while the results of LCI2.5 were similar in the two subgroups. The results of both populations are generally in line with the overall group. In both groups, the observed improvements were considered clinically relevant demonstrating an effect of ELX/TEZ/IVA.

Dosing regimen

The investigated dosing regimen used in study 111 is different than the proposed recommended dose in the SmPC as in the SmPC no lower limit of weight is proposed. Therefore, the safety in children with a weight < 10 kg is unknown. CF Foundation (CFF) Patient Registry data indicates that only a small minority of the children 2 through 5 years of age will have a weight < 10 kg, while it will still be close to the investigated 10 kg. However, it needs to be justified that the lower weight cut-off applies to the European population. Based

on the 2021 annual report of the European Cystic Fibrosis Society Patient Registry (ECFSPR), it can be assumed that there are underweight children in the range from 2 to 5 years weighing less than 10 kg. As exposure data show that the % increase for all the analytes at weight at 9.5 kg was approximately 4%, the expected increase in AUCtau would be 24% in a child weighing 7 kg. The applicant argued that the weight of 7 kg is not representative of this age group based on EU registry data. Instead, the applicant refers to 2021 ECFSPR Annual Report, in which for CF patients 2 to 5 years of age the median BMI z-score range of approximately -1.5 to 0.75. Further calculations were then based on BMI z-score for age and weight for age chart. These would prove that no children would have a weight under 10 kg. However, the use of the range (across the countries) of *median* BMI is not considered. This means that 25% of patients could have a BMI below -1.5 and thus a weight below the argued corresponding weight of 10 kg. Moreover, the calculations of the applicant are based on the assumption that weight will follow the same percentile as BMI, which can be questioned because in CF growth is generally affected. As these calculations are based on questionable assumptions, it is uncertain whether the weight of 2-year-old children with CF is adequately identified. Provided simulations for subjects weighing 7 kg demonstrated that the percent increase for all analytes is expected to be approximately 30% greater (with M1-TEZ being approximately 35% greater) than the simulated exposures for children weighing 10 kg. Therefore, a lower weight limit of 10 kg is proposed by CHMP in the dosing recommendation of section 4.2 of the SmPC similarly to the studied subjects included in Part B of Study 111. This was accepted by the MAH.

It remains unclear as to the optimal age in F-heterozygotes to start Kaftrio considering that the indication of Kaftrio is broad including patients with severe CF as well as patients with less severe CF. In that light a post-approval efficacy study for children that are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio was considered necessary. Such a study is less relevant in F/F homozygotes given that a PAES with another CFTR modulator Orkambi is already ongoing in the young patient population albeit that this will be with LUM/IVA and not ELX/TEZ/IVA.

The MAH argued that 1) the benefits of early initiation with CFTR modulators have been demonstrated across multiple modulators, age groups, and genotypes through clinical studies, 2) CFTR modulators, including ELX/TEZ/IVA, treat the underlying mechanism of CF, and the treatment effect should be the same regardless of genotype. Furthermore, the MAH considered that the benefits of early initiation of CFTR modulators in patients with severe CF as well as patients with less severe CF are sufficiently supported by real-world data from the Kalydeco PAES (Study VX15-770-125) and the Orkambi PAES (Study VX18-809-128).

However, in the CHMP view, the ongoing post-authorisation efficacy studies for Kalydeco and Orkambi in children 2 through 5 years will only provide further insight for children with a gating mutation (Class III) and children who are homozygous for F508del (Class II), respectively. These mutations are traditionally considered to cause severe CF. No further data will become available for subjects with residual function (F/RF mutations) with generally less burden of CF and a better prognosis through the ongoing PAES studies. Additionally, no longitudinal data will become available for subjects with F/MF mutations, although there is less question for these subjects with severe CF than those with less severe CF regarding the optimal age to start treatment. Therefore, a PAES study is considered relevant to provide further efficacy information especially in the less severe population such as the F/RF population.

A future PAES in all children who are F heterozygotes (aged 2-5 years) receiving treatment with Kaftrio will provide further valuable information regarding the magnitude of effect in the real world that is not already gathered through other studies. The MAH committed to perform a post-approval efficacy study (PAES) for children that are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio. The proposed study will investigate the long-term effectiveness comparing disease progression among children with CF who

are heterozygous for F508del-CFTR and are aged 2 through 5 years at the time of Kaftrio treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kaftrio treatment, in addition to a longitudinal historical cohort. The following cohorts will be defined:

- Kaftrio cohort: countries with commercial access to Kaftrio during enrolment period
- Matched cohort: countries without commercial access to Kaftrio during enrolment period
- Longitudinal historical cohort: same as Kaftrio.

A Matched Concurrent Comparator Cohorts of children who have never received Kaftrio (or other CFTR modulator) treatment, and who are having 2 mutations that results in minimal CFTR function that are not F508 mutations (MF/MF) should also be considered. Moreover, it is suggested to include a subgroup analysis by prior modulator treatment. The detailed protocol of the PAES will be submitted to the EMA within 6 months of CHMP opinion which is acceptable.

2.6.7. Conclusion on clinical efficacy

The efficacy of ELX/TEZ/IVA in children from 2 to 5 years of age was a secondary objective of Study 111 Part B. The observed results in Study 111 further supported the benefit of ELX/TEZ/IVA in CF subjects 2 through 5 years of age.

The CHMP agreed that partial extrapolation concepts can be applied for the assessment of the clinical data in this young age population.

This is based on :

1)the similarity of the underlying pathophysiology of CF adults and paediatric patients,

2) the fact that PK exposures in patients from 2 to 5 years of age were within or generally within the range observed in subjects ⩾18 years of age,

3) the effect in the SwCl being similar to the older ages group, efficacy in patients from 2 to 5 years of age can be partially extrapolated from data from the Phase 3 studies in CF subjects ⩾6 years of age.

Consistent with the efficacy demonstrated in subjects ⩾6 years of age, a clinically improvement in SwCl, was observed. Other clinical parameters were supportive of efficacy. Collectively, these efficacy data support the benefit of ELX/TEZ/IVA in CF subjects 2 through 5 years of age.

Provided simulations for subjects weighing 7 kg demonstrated that the percent increase for all analytes is expected to be approximately 30% greater (with M1-TEZ being approximately 35% greater) than the simulated exposures for children weighing 10 kg. Therefore, upon CHMP's request, a lower weight limit of 10 kg was added in the dosing recommendation of section 4.2 of the SmPC similarly to the studied subjects included in Part B of Study 111.

However, as the efficacy data remain limited in certain mutations in particular for less severe patients with F/RF mutations and the unanswered question of the optimal age to start Kaftrio, the CHMP requested the MAH to perform a PAES study and collect efficacy data post-approval for children that are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio.

The MAH shall complete, within the stated timeframe, the below measures related to the PAES study :

Description	Due date
Post Authorisation Efficacy Study (PAES): Post-authorisation efficacy In order to further characterise the long-term efficacy among children with CF who are heterozygous for *F508del* and aged 2 through 5 years, the MAH should conduct and submit the results of a long-term effectiveness registry-based study comparing disease progression among children with CF who are heterozygous for F508del-CFTR and are aged 2 through 5 years at the time of Kaftrio treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kaftrio treatment, in addition to a longitudinal historical cohort, according to an agreed protocol.	Full protocol submission by June 24 Enrolment completed by Dec 2024 Final report Due date 31 Dec 2029

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Part A

A total of 18 subjects received at least 1 dose of study drug in the Part A Treatment Period, with a mean exposure of 15.0 days.

Part B

A total of 75 subjects received at least 1 dose of study drug in the Part B Treatment Period, with a mean exposure of 23.8 weeks (Table 15).

Table 15: Summary of Exposure (Safety Set, Part B)

	ELX/TEZ/IVA N = 75
Total exposure (patient weeks)	1785.0
Total exposure (patient years)	37.2
Exposure duration (weeks)	
n	75
Mean (SD)	23.8 (2.4)
Median	24.1
Min, max	4.6, 26.4
Exposure duration by interval, n (%)	
≤15 days	0
>15 days to ≤4 weeks	0
>4 to ≤8 weeks	1 (1.3)
>8 to ≤12 weeks	0
>12 to ≤16 weeks	0
>16 to ≤20 weeks	1 (1.3)
>20 to ≤24 weeks	33 (44.0)
>24 weeks	40 (53.3)

Source: Table 14.1.7b
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects. Duration of study drug exposure (weeks) = (last dose date in Part B – first dose date in Part B + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = (last dose date in Part B – first dose date in Part B + 1)/336, regardless of study drug interruption; 336 days = 48 weeks.

2.6.8.2. Adverse events

Part A

Fifteen (83.3%) subjects had at least 1 AE. All AEs were mild or moderate in severity, and no subjects had severe or life-threatening AEs. Five subjects (27.8%) had a related AE. There were no deaths or serious AEs. One (5.6%) subject interrupted study drug due to AEs. There were no discontinuations due to AEs.

Part B

Seventy-four (98.7%) subjects had at least 1 AE. All AEs were mild or moderate in severity, and no subjects had severe or life-threatening AEs. Two (2.7%) subjects had SAEs. One (1.3%) subject discontinued study drug due to AEs, and 5 (6.7%) subjects interrupted study drug due to AEs. There were no deaths.

Table 16: Overview of AEs (Safety Set, Part B)

Category	ELX/TEZ/IVA N = 75 n (%)
Number of AEs (total)	485
Subjects with any AEs	74 (98.7)
Subjects with AEs by strongest relationship	
Not related	15 (20.0)
Unlikely related	27 (36.0)
Possibly related	32 (42.7)
Related	0
Subjects with AEs by maximum severity	
Mild	47 (62.7)
Moderate	27 (36.0)
Severe	0
Life-threatening	0
Death	0
Subjects with AEs leading to study drug discontinuation	1 (1.3)
Subjects with AEs leading to study drug interruption	5 (6.7)
Subjects with Grade 3/4/5 AEs	0
Subjects with related AEs[a]	32 (42.7)
Subjects with SAEs	2 (2.7)
Subjects with related SAEs[a]	1 (1.3)
Subjects with AEs leading to death	0

Source: Table 14.3.1.1b

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

[a] When summarizing number of subjects with related AEs and SAEs, AEs with relationship of related, possibly related, and missing were counted.

Incidence of adverse events

Part A

Overall, the AEs were mostly consistent with common manifestations or complications of CF disease in CF subjects 2 through 5 years of age or with the known safety profile of ELX/TEZ/IVA.

Part B

AEs that occurred in ≥5% of subjects are summarized by PT in Table 17.

The most common AEs (≥10% incidence overall) by PT were cough, pyrexia, rhinorrhea, vomiting, COVID-19, nasal congestion, rash, upper respiratory tract infection, decreased appetite, ALT increased, and infective pulmonary exacerbation (PEx) of CF. Overall, the AEs were mostly consistent with common manifestations or complications of CF disease in CF subjects 2 through 5 years of age or with the known safety profile of ELX/TEZ/IVA.

Table 17: AEs Occurring in At Least 5% of Subjects by PT (Safety Set, Part B)

Preferred Term	ELX/TEZ/IVA N = 75 n (%)
Subjects with any AEs	74 (98.7)
Cough	46 (61.3)
Pyrexia	26 (34.7)
Rhinorrhea	25 (33.3)
Vomiting	21 (28.0)
COVID-19	14 (18.7)
Nasal congestion	13 (17.3)
Rash	12 (16.0)
Upper respiratory tract infection	11 (14.7)
Decreased appetite	9 (12.0)
ALT increased	8 (10.7)
Infective PEx of CF	8 (10.7)
Headache	7 (9.3)
SARS-CoV-2 test positive	7 (9.3)
Constipation	6 (8.0)
Nasopharyngitis	6 (8.0)
Abdominal discomfort	5 (6.7)
Diarrhea	5 (6.7)
Abdominal pain	4 (5.3)
AST increased	4 (5.3)
GGT increased	4 (5.3)
Irritability	4 (5.3)

Source: Table 14.3.1.3b

Severity of Adverse Events

Part A

All AEs were mild (66.7%) or moderate (16.7%) in severity, and no subjects had severe or life-threatening AEs. There were no Grade 3/4/5 AEs.

Part B

All AEs were mild (62.7%) or moderate (36.0%) in severity, and no subjects had severe or life-threatening AEs. (Table 16). Two (2.7%) subjects had SAEs. There were no Grade 3/4/5 AEs.

Relationship of Adverse Events

Part A

One (5.6%) subject had AEs that were assessed by the investigator as related to study drug, and 4 (22.2%) subjects had AEs that were assessed by the investigator as possibly related.

Most frequent related AEs were ALT increased, and AST increased for each 2 events (11.1%).

Alanine aminotransferase increased	2 (11.1)
Aspartate aminotransferase increased	2 (11.1)

Part B

No subjects had AEs that were assessed by the investigator as related to study drug, and 32 (42.7%) subjects had AEs that were assessed by the investigator as possibly related.

Table 18: Related AEs Occurring in At Least 2% of Subjects by PT (Safety Set, Part B)

Preferred Term	ELX/TEZ/IVA N = 75 n (%)
Subjects with any related AEs	32 (42.7)
Cough	8 (10.7)
Alanine aminotransferase increased	7 (9.3)
Rash	4 (5.3)
Aspartate aminotransferase increased	3 (4.0)
Aggression	3 (4.0)
Irritability	3 (4.0)
Psychomotor hyperactivity	3 (4.0)
Gamma-glutamyltransferase increased	2 (2.7)
Rhinorrhoea	2 (2.7)
Frequent bowel movements	2 (2.7)
Headache	2 (2.7)
Decreased appetite	2 (2.7)

Source: Study 111 CSR/Table 14.3.1.4b

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor

Notes: AEs were coded using MedDRA version 25.0. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT. When

Adverse Events of Special Interest

AESIs were defined as AEs of elevated transaminases and AEs of rash

Part A

Elevated Transaminase Events

Three (16.7%) subjects had nonserious elevated transaminase events, all of which were assessed by the investigator as moderate in severity, and none of which led to study drug interruption or discontinuation.

Rash Events

Four (22.2%) subjects had a total of 6 nonserious rash events. All events were assessed by the investigator as mild in severity. None of the events was serious or led to study drug interruption or discontinuation. All rash events had an outcome of being resolved.

Part B

Elevated Transaminase Events

Eight (10.7%) subjects had elevated transaminase events.

All of the events were mild or moderate in severity. None of the events was serious or led to treatment discontinuation. Elevated transaminase events led to treatment interruption in 1 (1.3%) subject. The elevated transaminase events had a mean (SD) duration of 24.8 (24.8) days, and the mean (SD) time-to-onset of the first event was 50.0 (52.0) days.

Rash Events

Fifteen (20.0%) subjects had at least 1 rash event. All rash events were mild or moderate in severity; none were serious. Twelve of the 15 subjects had rash events that were assessed by the investigator as not related or unlikely related to the study drug or were confounded by concurrent viral symptoms. Two subjects had rash events that led to treatment interruption, both of whom resumed the study drug without recurrence of the rash. There were no study drug discontinuations due to rash events.

By sex, 4 (9.8%) female subjects and 11 (32.4%) male subjects had a rash.

2.6.8.3. Serious adverse events, deaths, and other significant events

Deaths

There were no deaths in Part A or Part B.

Serious adverse events

Part A

No subjects had SAEs.

Part B

Two (2.7%) subjects had SAEs:

- One subject had concurrent SAEs of anal incontinence (mild in severity), urinary incontinence (moderate in severity), and abnormal behaviour (moderate in severity). The subject was 3 years of age. On Study Day 66, the subject had behavioural changes (hyperactivity and aggression) with increased urinary urgency and enuresis. From Study Days 80 to 113, the study drug was interrupted and resumed twice, with reported improvement of symptoms within 1 to 2 days upon study drug interruption and return of symptoms within 1 to 2 days upon resumption. The study drug was discontinued on Study Day 127. The investigator did not consider the subject’s behavioural changes outside of what is typically seen in the subject's age group but assessed these events as possibly related to the study drug.

- One subject had an SAE of infective PEx of CF that was assessed by the investigator as moderate in severity and not related to the study drug; the event did not lead to a change in study drug dosing and was resolved.

2.6.8.4. Laboratory findings

Chemistry

Part A

There were 4 (22.2%) subjects with ALT or AST >3 × ULN, 3 (16.7%) of whom had ALT or AST >5 × ULN, and 1 (5.6%) of whom had ALT or AST >8 × ULN; all of these subjects had elevated ALT at screening or Day 1. There were no subjects with ALT or AST >3 × and total bilirubin >2 × ULN.

Part B

Nine (12.0%) subjects had AEs related to chemistry findings (excluding LFT and CK results); all of these AEs were mild or moderate in severity, and none led to treatment interruption or discontinuation.

Liver Function Tests

The majority of subjects had ALT and AST values that remained ⩽3 × ULN. Six (8.0%) subjects had ALT or AST >3 × ULN, 2 (2.7%) subjects had ALT or AST >5 × ULN, and 1 (1.3%) subject had ALT or AST >8 × ULN. No subjects had total bilirubin >2 × ULN.

Table 19: Threshold Analysis of LFT Chemistry (Safety Set, Part B)

Parameter Subjects with Non-missing Post-baseline Data Post-baseline Threshold Analysis Criteria, n (%)	ELX/TEZ/IVA N = 75
ALT (U/L)	
Total, N1	75
>ULN to ≤3 × ULN	44 (58.7)
>3 × to ≤5 × ULN	4 (5.3)
>5 × to ≤8 × ULN	1 (1.3)
>8 × to ≤20 × ULN	1 (1.3)
>20 × ULN	0
>3 × ULN	6 (8.0)
>5 × ULN	2 (2.7)
>8 × ULN	1 (1.3)
AST (U/L)	
Total, N1	75
>ULN to ≤3 × ULN	14 (18.7)
>3 × to ≤5 × ULN	1 (1.3)
>5 × to ≤8 × ULN	0
>8 × to ≤20 × ULN	0
>20 × ULN	1 (1.3)
>3 × ULN	2 (2.7)
>5 × ULN	1 (1.3)
>8 × ULN	1 (1.3)

ALT (U/L) or AST (U/L)	
Total, N1	75
(ALT>ULN to ≤3 × ULN) or (AST>ULN to ≤3 × ULN)	45 (60.0)
(ALT>3 × to ≤5 × ULN) or (AST>3 × to ≤5 × ULN)	4 (5.3)
(ALT>5 × to ≤8 × ULN) or (AST>5 × to ≤8 × ULN)	1 (1.3)
(ALT>8 × to ≤20 × ULN) or (AST>8 × to ≤20 × ULN)	0
ALT>20 × ULN or AST>20 × ULN	1 (1.3)
(ALT>3 × ULN) or (AST>3 × ULN)	6 (8.0)
(ALT>5 × ULN) or (AST>5 × ULN)	2 (2.7)
(ALT>8 × ULN) or (AST>8 × ULN)	1 (1.3)
Total bilirubin (µmol/L)	
Total, N1	75
>ULN to ≤1.5 × ULN	6 (8.0)
>1.5 × to ≤2 × ULN	1 (1.3)
>2 × to ≤3 × ULN	0
>3 × to ≤10 × ULN	0
>10 × ULN	0
Direct bilirubin (µmol/L)	
Total, N1	75
>ULN to ≤1.5 × ULN	2 (2.7)
>1.5 × to ≤2 × ULN	0
>2 × to ≤3 × ULN	0
>3 × to ≤10 × ULN	0
>10 × ULN	0
Indirect bilirubin (µmol/L)	
Total, N1	72
>ULN to ≤1.5 × ULN	8 (11.1)
>1.5 × to ≤2 × ULN	0
>2 × to ≤3 × ULN	1 (1.4)
>3 × to ≤10 × ULN	0
>10 × ULN	0
(ALT or AST) and TBILI	
Total, N1	75
(ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN	0
ALP (U/L)	
Total, N1	75
>ULN to ≤1.5 × ULN	27 (36.0)
>1.5 × to ≤2.5 × ULN	3 (4.0)
>2.5 × to ≤5 × ULN	0
>5 × to ≤20 × ULN	0
>20 × ULN	0

GGT (U/L)	
Total, N1	75
>ULN to ≤2.5 × ULN	10 (13.3)
>2.5 × to ≤5 × ULN	2 (2.7)
>5 × to ≤20 × ULN	2 (2.7)
>20 × ULN	0

Source: Table 14.3.4.1.2b

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; GGT: gamma-glutamyl transferase; IVA: ivacaftor; LFT: liver function test; n: number of subjects in the post-baseline category; N: total sample size; N1: number of subjects with at least 1 non-missing measurement during the TE Period in Part B; TBILI: total bilirubin; TE: treatment-emergent; TEZ: tezacaftor; ULN: upper limit of normal

Note: Within each parameter, a subject was counted in all applicable post-baseline categories based on the worst assessment during the TE Period in Part B. Percentages were evaluated as n/N1. Threshold criteria involving 2 LFT parameters could be determined by assessments at different visits during the TE Period in Part B.

Creatine Kinase

The mean (SD) increase in CK ranged from 25.7 (82.4) U/L at Day 15 to 41.7 (47.3) U/L at Week 20. The majority of subjects had CK levels ≤2 × ULN; no subjects had CK levels >5 × ULN.

AEs of CK elevation occurred in 1 (1.3%) subject.

Haematology

In Part A and Part B, there were no trends observed in haematology parameters. No subjects had AEs related to haematology findings in part A. Two (2.7%) subjects had AEs related to haematology findings, i.e. Neutrophil count decreased 1 (1.3%), and Platelet count increased 1 (1.3%) in Part B.

Coagulation

No trends were observed in coagulation parameters in Part A and Part B. In addition, no subjects had AEs related to coagulation findings.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs, Pulse Oximetry, Electrocardiogram, Physical examination

No trends were observed in the vital signs parameters, pulse oximetry, ECG parameters and physical examination. No subjects had AEs related to finding in vital signs, pulse oximetry, ECG or physical examination in Part A or Part B.

Table 20 Threshold Analysis of ECGs during the Treatment-emergent Period - Part B Safety Set

Parameter Subjects with Non-missing Post-baseline Data Post-baseline Threshold Analysis Criteria, n (%)	ELX/TEZ/IVA N = 75
ECG mean heart rate (beats/min)	
Total, N1	75
Bradycardia	
<55 beats/min	0
Tachycardia	
>134 beats/min	2 (2.7)
PR interval, single beat (msec)	
Total, N1	75
>180 msec and increase from baseline ≥20 msec	0
QRS duration, single beat (msec)	
Total, N1	75
>89 msec	5 (6.7)
QTcF interval, single beat (msec)	
Total, N1	75
>449 msec	0
≥500 msec	0
Increase from baseline >60 msec	0

- N1: number of subjects with at least one non-missing measurement during the treatment-emergent period in Part B.

- n (%): n is the number of subjects in the post-baseline category; within each parameter, a subject is counted in all applicable post-baseline categories based on the worst assessment during the treatment-emergent period in Part B; percentage is n/N1.

Ophthalmologic Examinations

No subjects had an AE of cataract; in Part B 1 (1.3%) subject had a nonserious AE of lenticular opacities that was characterized as mild in severity and did not lead to treatment interruption or discontinuation.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

The main study is a paediatric study that includes children 2 through 5 years of age only and described as the main study. No further studies in special populations are submitted.

2.6.8.7. Immunological events

N/A

2.6.8.8. Safety related to drug-drug interactions and other interactions

The main study is a paediatric study that includes children 2 through 5 years of age only and described as the main study. No further discussion on safety related to drug-drug interactions or other interactions is provided, which can be agreed.

2.6.8.9. Discontinuation due to adverse events

Adverse Events that led to Discontinuation of Study Drug

Part A

No subjects had AEs that led to discontinuation of the study drug.

Part B

One (1.3%) subject had an SAE of abnormal behaviour that led to discontinuation of the study drug.

The event was moderate in severity and assessed by the investigator as possibly related to the study drug. The study drug was withdrawn, and the events resolved in a few days.

Adverse Events that led to Interruption of Study Drug

Part A

One (5.6%) subject had AEs of hyperamylasemia and hyperlipasemia of that led to treatment interruption. The AEs were mild in severity and assessed by the investigator as not related to the study drug. The AEs resolved, the subject resumed ELX/TEZ/IVA, and completed dosing.

Part B

Five (6.7%) subjects interrupted their study drug due to AEs.

- Two subjects interrupted the study drug due to AEs of rash. Both rash events were moderate in severity; one was assessed by the investigator as possibly related to the study drug, and the other as unlikely related to the study drug. The events resolved, and both subjects resumed the study drug with no recurrence of the rash.
- One subject interrupted study drug due to concurrent SAEs of anal incontinence and urinary incontinence. The SAE of anal incontinence was mild in severity and the SAE of urinary incontinence was moderate in severity. Both SAEs were assessed by the investigator as possibly related. The events resolved, and the study drug was resumed.
- One subject interrupted the study drug due to an AE of aggression, which was moderate in severity and assessed by the investigator as possibly related. The event was resolved, and the study drug was resumed with no recurrence of the event.
- One subject interrupted the study drug due to AEs of ALT, AST, and GGT increased, which were all mild in severity and assessed by the investigator as not related. The subject enrolled in an open-label extension study on study drug interruption.

2.6.8.10. Post marketing experience

As of 20 July 2022, it is estimated that 57,577 patients (representing 70,506 person-years) have been exposed to ELX/TEZ/IVA worldwide through commercial access or compassionate use programs. Of these 57,577 patients, 25,687 were from US commercial use.

2.6.9. Discussion on clinical safety

The safety data set to support the application in children aged 2 through 5 years of age is provided by the single-arm, open-label study VX20-445-111, where 18 (Part A) and 75 (Part B) patients were treated for 2 weeks and 24 weeks, respectively. The mean exposure was 23.8 weeks (part B). As the provided safety data set is limited to support chronic use, extrapolation of the safety results obtained in children 6 through 11 years of age and the data obtained in adults and adolescents are also supporting this application.

ELX/TEZ/IVA was generally well tolerated by children 2 through 5 years of age up to 24 weeks, as shown by the reported low number of serious adverse events (0% in part A, 2.7 % in Part B), treatment interruptions (5.6% in Part A, 6.7% in Part B) and treatment discontinuations due to AE (0% in Part A, 1.3% in Part B). Overall, these findings are in line with the findings in children 6 through 11 years of age and the data obtained in adults and adolescents.

Adverse events, related adverse events, serious adverse events and deaths

In Part A, all AEs were mild or moderate in severity, and no subjects had severe or life-threatening AEs. Five subjects (27.8%) had a related AE. In Part B, seventy-four (98.7%) subjects had at least 1 AE. All AEs were mild or moderate in severity, and no subjects had severe or life-threatening AEs.

The most common AEs (⩾10% incidence overall) by PT were cough, pyrexia, rhinorrhea, vomiting, COVID-19, nasal congestion, rash, upper respiratory tract infection, decreased appetite, ALT increased, and infective pulmonary exacerbation (PEx) of CF. The AEs were mostly likely connected with manifestations or complications of CF, common illness in subjects 2 through 5 years of age or with the known safety profile of ELX/TEZ/IVA.

In Part A, one (5.6%) subject had AEs that were assessed by the investigator as related to the study drug, and 4 (22.2%) subjects had AEs that the investigator assessed as possibly related.

In Part B, no subjects had a related AEs and 32 (42.7%) subjects had AEs that were assessed by the investigator as possibly related. The number of treatment-related adverse events (related and possibly related) is consistent with the pivotal study 102 (47.6%) and study 106 Part B in children 6 through 11 years of age (50%). In part B, the related AEs were mostly consistent with the known safety profile of ELX/TEZ/IVA.

Related AEs were dominated by cough (10.7%), ALT increased (9.3%), rash (5.3%) and AST (4.0%). Next, AEs in SOC Psychiatric disorder were frequently observed, i.e., the PTs aggression, irritability and psychomotor hyperactivity, each 4%.

In children 6 through 11 years of age, behavioural AEs were also observed; these were aggression, anxiety (3%) and depressed mood (1.5%). Aggression and irritability occur more often in children of 2-5 years compared to 6-11 years. Because of the relatively low number of patients in the studies, the low incidence of the AEs and the absence of a placebo arm, it is not possible to draw a firm conclusion. However, the numbers are higher than in the adult/adolescent population (abnormal dreams, anger and libido decreased, each 0.5%).

There are no analyses of de-challenge or positive rechallenge of the identified cases. Currently, there are three post-authorisation studies in the pharmacovigilance plan for the safety concern "use in children aged 2 to 11 years", the ongoing PASS (final report 2025), study 107 with the interim analysis report in February 2023 and the open-label extension study (study 112), which will be finalised in June 2025. In addition to

these already planned activities, the MAH has confirmed to monitor and analyse psychiatric-related AEs in the PSURs for all -patients groups in the 3 age categories.

Only in Part B, 2 (2.7%) SAEs were observed, one subject of 3 years of age with concurrent SAEs of anal incontinence, urinary incontinence, and abnormal behaviour. The investigator did not consider the subject's behavioural changes outside of what is typically seen in the subject's age group but assessed these events as possibly related to the study drug. Another subject had an SAE of infective PEx of CF that was assessed by the investigator as moderate in severity and not related to study drug. Overall, the number of SAEs is low, consistent with the finding in children 6 through 11 years of age and lower than in adults and adolescents and therefore supportive for safety.

There were no deaths in study 111.

Adverse events of specific interest

AESIs were defined as AEs of elevated transaminases and AEs of rash.

In Part A, three (16.7%) subjects had nonserious elevated transaminase events, all moderate in severity, none of which led to studying drug interruption or discontinuation. In Part B, eight (10.7%) subjects had elevated transaminase events, specifically, 8 (10.7%) subjects had ALT increased, and 4 (5.3%) subjects AST increased. None of the events was serious or led to treatment discontinuation, while in 1 (1.3%) subject led to treatment interruption. To be included in part B of Study 111, subjects must have had no elevated serum ALT or AST ≥3 x ULN or total bilirubin ≥2 x ULN at screening and in the previous year; the latter was not an exclusion criterion in the other studies. This may have led to the inclusion of healthier subjects. Despite the more stringent exclusion criteria, the incidences of AE of ALT or AST elevations were quite similar, while threshold analyses indicate a trend of more events. Nevertheless, this is not considered worrisome because elevation of ALT and AST are more common in children compared to adults. Therefore, no further action is required as section 4.4 the SmPC currently recommends monitoring of transaminases (ALT and AST) and total bilirubin prior to initiating treatment every 3 months during the first year of treatment and annually thereafter for all patients.

The number of ALT increased is similar to the number in subjects 6 through 11 years of age (7 (10.6%)) and to the number in adults and adolescents (20 (9.9.%)) in study 102. However, as the frequency is higher in children 2 through 5 years of age and in children 6 through 11 years of age, the table in section 4.8 has been updated to frequency very common (> 1/10) for ALT increased.

Regarding rash, 4 (22.2%) subjects had a total of 6 nonserious rash events in Part A, while 15 (20.0%) subjects in Part B. This is generally similar to the subjects 6 through 11 years of age and higher than in the adults and adolescents. However, rash occurs frequently in young children as symptoms of a common viral disease of the youth.

These ADRs are described in the paediatric part of section 4.8 of the SmPC.

Discontinuations and disruptions of medication

Only in Part B 1 subject discontinued due to an SAE of abnormal behaviour.

Regarding disruption of medication, in Part A 1 (5.6%) subject interrupted medication because of unrelated AEs of hyperamylasemia and hyperlipasemia. In Part B, 5 (6.7%) subjects interrupted the study drug due to AEs i.e., 2 subjects with rash, 1 subject with anal and urinary incontinence, 1 subject because of aggression, and 1 subject because of elevation of AEs of ALT, AST, and GGT.

The event of hyperamylasaemia and hyperlipasaemia considered unrelated to study drug indicates involvement of the pancreas, one of the earliest- and most commonly- affected organs in patients with cystic fibrosis. Therefore, the events can be considered a complication of CF.

The event of anal and urinary incontinence, assessed by the investigator as possibly related, occurred in the same subject as the aggression. The events resolved, and the study drug was resumed without reoccurring events. Behavioural changes, including incontinence in young children, are difficult to interpret. No further conclusions can be drawn from this one case. No further action is required for these cases. Increases in liver enzymes and rash are known effects of ELX/TEZ/IVA and have already been adequately addressed in the SmPC section 4.8.

Liver Function Tests

The findings are generally in line with the results found in the study in children 6 through 11 years of age and the studies in adults and adolescents, and there were 4 (22.2%) subjects in Part A and 6 subjects (8.0%) in Part B with ALT or AST >3 × ULN, 3 (16.7%) subjects of whom in Part A and 2 (2.7%) in Part B had ALT or AST >5 × ULN, and 1 (5.6%) of whom in Part A and 1 (1.3%) in Part B had ALT or AST >8 × ULN. No subjects had total bilirubin >2 × ULN. One patient had AST > 20 x ULN. Overall, the findings are in line with the known profile of ELX/TEZ/IVA.

A total of 5 subjects had QRS duration >89 msec on the ECG. For three of the five subjects, the prolongation of the QRS duration remained stable at subsequent visits, for the other two subjects QRS was prolonged on only one occasion, with all prior and subsequent ECG measurements in the normal range. Therefore, it can be concluded that for these subjects, the observed QRS prolongation was not related to Kaftrio.

One subject had an AE of lenticular opacity. In the other investigations, i.e., vital signs, pulse oximetry, physical examinations, no trends were observed, and no subjects had AEs related to any of the investigations.

2.6.10. Conclusion on clinical safety

The safety in subjects 2 through 5 years of age is based on the safety data set provided by the single-arm, open-label study VX20-445-111 and the extrapolation of safety data obtained in children 6 through 11 years of age and the data obtained in adults and adolescents.

ELX/TEZ/IVA was generally well tolerated by children 2 through 5 years of age up to 24 weeks, as shown by the reported low number of serious adverse events, treatment discontinuations and interruptions. The safety findings in subjects are generally in line with the known safety profile of ELX/TEZ/IVA and are similar to the findings in children 6 through 11 years of age and to adults and adolescents.

Nevertheless, safety data remain limited for this patient population. Safety data will also be collected and provide further safety information post approval. The OLE extension study is included in the RMP.

2.7. Risk management plan

2.7.1. Safety concerns

The summary of safety concerns are detailed below:

Table 21: Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

Table 22: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Open-label extension study **(Study 105)** Ongoing	Evaluate the long-term safety, tolerability, and efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in subjects 12 years of age and older with CF, homozygous or heterozygous for the F508del-CFTR mutation	Susceptibility for influenza virus infections Hepatotoxicity Cataract Long-term safety	Final Report	31 December 2022

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PASS Ongoing	Evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting	Susceptibility for influenza virus infections Hepatotoxicity Use in patients with moderate or severe hepatic impairment Use in pregnant women Long-term safety Use in children aged 2 to 11 years	Annual Reports Final Report	31 December 2021/2022/ 2023/2024 31 December 2025
Open-label extension study (Study 107) Ongoing	Evaluate the long-term safety, tolerability, efficacy, and the PD of ELX/TEZ/IVA treatment for 96 weeks in CF subjects 2 years of age and older, homozygous for F508del-CFTR mutation or heterozygous for F508del-CFTR and a minimal function mutation	Susceptibility for influenza virus infections Hepatotoxicity Cataract Long-term safety Use in children aged 2 to 11 years	Final Report	February 2023
Open-label extension study **(Study 112)** Ongoing	Evaluate the long-term safety, tolerability, efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in CF subjects 2 years of age and older	Susceptibility for influenza virus infections Hepatotoxicity Cataract Long-term safety Use in children aged 2 to 11 years	Final Report	June 2025

Plans for Post Authorisation Efficacy studies

Study status	Summary of Objective	Efficacy uncertainties addressed	Milestone	Due date:

Efficacy studies which are conditions of the MA				
Study number (TBD)	To evaluate disease progression among children with CF who are heterogenous for F*508Del* and aged 2 through 5 years at the time of ELX/TEZ/IVA initiation	Long Term efficacy among children with CF who are heterogenous for F*508Del* and aged 2 through 5 years at the time of ELX/TEZ/IVA initiation	Protocol submission	31 March 2024
Efficacy studies which are specific obligations in the context of conditional MA				
None/NA				

2.7.3. Risk minimisation measures

Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Susceptibility for influenza virus infections	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) (Final Report: 31 December 2022) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 107) (Final Report: February 2023) • Open-label extension study (Study 112) (Final Report: June 2025)

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 liver damage and worsening of liver function in patients with severe liver disease, expectations for LFT monitoring and detection of potential signs of liver problems are discussed. 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 (Study 105) (Final Report: 31 December 2022) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 107) (Final Report: February 2023) • Open-label extension study (Study 112) (Final Report: June 2025)
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 (Study 105) (Final Report: 31 December 2022) • Open-label extension study (Study 107) (Final Report: February 2023) • Open-label extension study (Study 112) (Final Report: June 2025)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and lactating women	**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:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Long-term safety	**Routine risk minimisation measures:** SmPC Section 4.8 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 (Study 105) (Final Report: 31 December 2022) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 107) (Final Report: February 2023) • Open-label extension study (Study 112) (Final Report: June 2025)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with moderate or severe hepatic impairment	**Routine risk minimisation measure:** SmPC Sections 4.2, 4.4, and 5.2 SmPC Sections 4.2 and 4.4 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:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Use in children aged 2 to 11 years	**Routine risk minimisation measure:** SmPC Sections 4.1, 4.2, and 4.4 PL Sections 1 and 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Open-label extension study (Study 107) (Final Report: February 2023) Open-label extension study (Study 112) (Final Report: June 2025) PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)

2.7.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 8.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the new indication in the 2 to 5 year of age and associated limited safety data in this population, the PRAC is of the opinion that the already existing entry in the EURD list for Kaftrio should follow a half-yearly cycle.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Updates made to the package leaflets for this procedure are minimal, and the structure and guidance for caregivers remains aligned to the principles agreed on in procedure EMEA/H/C/005269/0000.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kaftrio (ivacaftor / tezacaftor / elexacaftor) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It has an obligation to conduct post-authorisation efficacy studies [REG Art 9(4)(cc), Art 10a(1)(b), DIR Art 21a(f), Art 22a(1)(b)];

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for is: *Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1)*

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which and at present, there is no cure. Cystic fibrosis is caused by mutations in the CFTR gene that result in the absence or deficient function of the CFTR protein at the cell surface, which is

responsible for the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.

The aim of the therapy is to improve CFTR through the cell an at the cell surface resulting in an improvement in the target organs.

3.1.2. Available therapies and unmet medical need

CFTR modulators such as ELX/TEZ/IVA are currently important therapies for cystic fibrosis as they modify the progress of the disease by maintaining or improving the lung function, reducing the risk of exacerbations and improving quality of life. A second type of therapy is symptomatic therapy, which targets specific disease symptoms, such as nutritional supplements, antibiotics, and mucolytics.

Within the modulators, correctors (such as tezacaftor and elexacaftor) and potentiators (such as ivacaftor) are distinguished. While the correctors facilitate the cellular processing and trafficking of mutant CFTR to increase the quantity of functional CFTR at the cell surface, potentiators enhance the CFTR's channel gating activity, which is delivered to the cell surface. Modulator therapy improves chloride transport at the cell surface.

Kaftrio tablets in a combination regimen with ivacaftor 150 mg tablets is currently indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symkevi (tezacaftor/ivacaftor) are CFTR modulators approved for CF patients with specific mutations. Currently Kalydeco and Orkambi are authorised in very CF patients 2 through 5 years of age, (Kalydeco for specific gating mutation or R117H mutation and Orkambi in subjects with F/F mutation).

3.1.3. Main clinical studies

The main evidence of efficacy submitted is study 111, a phase 3, open-label, 2-part (Parts A and B), multicenter study in subjects 2 through 5 years of age. Study 111 is conducted in 2 parts (Parts A and B) in CF subjects 2 through 5 years of age who are heterozygous for F508del and a minimal function mutation (F/MF genotypes) or homozygous for F508del (F/F genotype). A total of 18 (Part A) and 75 (Part B) subjects were treated for 2 weeks and 24 weeks, respectively.

The results of the bioequivalence Study 012 in healthy adult subjects to support the use of granules in Study 111, simulations and the updated popPK models, which included PK data from adults and adolescents, were used to select a dosing regimen for study 111 Part B.

The following total daily dose of ELX/TEZ/IVA for patients 2 through 5 years of age was evaluated, i.e.

- Patients weighing ≥14 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h
- Patients weighing ≥10 kg to <14 kg: ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg qAM, 59.5 mg qPM

The primary objective was safety; efficacy was the secondary objective.

The secondary endpoints included Lung Clearance Index ($LCI_{2.5}$), sweat chloride (SwCl). Other endpoints included growth parameters, including z-scores.

The extension of the indication to children 2 through 5 years old is based on the principle of partial extrapolation from adults and adolescents to paediatric patients. Consistent with the principles described in ICH E11 and EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018), extrapolation of efficacy from older to younger paediatric patients may be

possible when 1) a medicinal product is to be used in younger paediatric patients for the same indication as those studied in older paediatric patients, 2) the disease process is similar, and 3) the outcome of therapy is likely to be comparable. In CF, the disease process in all age groups stems from a common aetiology of dysfunctional CFTR protein that is targeted by ELX/TEZ/IVA and because ELX/TEZ/IVA targets the dysfunctional CFTR, and the outcome of therapy in younger age group is expected to be comparable to adults.

A popPK modelling approach was used to describe the exposures of the three drugs in children aged 2-5 years due to sparse blood sampling performed in study 111.

3.2. Favourable effects

PopPK simulations results demonstrated that under the studied dosing regimen with a 14 kg weight cutoff, the exposures of all compounds, including their metabolites, were within the 5th to 95th percentile of the observed exposure range for subjects ≥18 years of age for both weight groups; although the median of the ELX exposures was below the median seen in adults.

Treatment with ELX/TEZ/IVA resulted in the LS mean absolute change in SwCl from baseline through Week 24 of -57.9 mmol/L (95% CI: -61.3, -54.6; P<0.0001). This reduction is generally comparable to the observed reduction in the children aged 6 through 11 years of age (LS mean difference from baseline -60.9 mmol/L (95% CI: -63.7, -58.2) as well as in the adult and adolescent population (LS mean difference from baseline - 41.8 mmol/L (95% CI: -44.4, -39.3) and -45.1 mmol/L (95% CI: -50.1, -40.1) in patients with F/MF mutations and with F/F mutations, respectively). Treatment with ELX/TEZ/IVA resulted in an improvement in ventilation inhomogeneity measured by LCI2.5; the LS mean absolute change in LCI2.5 from baseline through Week 24 was -0.83 (95% CI: -1.01, -0.66; P<0.0001 and the yearly event rate for Pex was 0.32.

Subgroup analyses for different patient groups (F/F or F/MF) showed that the results in SwCl were somewhat better in the F/F patients.

Growth parameters normalised for age were stable or showed an improvement; LS mean absolute changes from baseline at Week 24 were for weight z-score: 0.02 (95% CI: -0.04, 0.09), for height z-score: -0.06 (95% CI: -0.11, 0.00) and BMI z-score: 0.10 (95% CI: 0.00, 0.20).

Also, improvements were observed for the markers of pancreatic function and inflammation.

3.3. Uncertainties and limitations about favourable effects

The number of patients is limited, but all but 1 patient finalized the treatment.

Only subjects with the F/MF genotype and F/F genotype were enrolled, while the indication allows for a broader population. However, studies that included adults and adolescents have proved that the effects observed in the population with the F/MF genotype or F/F genotype are similar to other genotypes that have at least one F508del mutation. Therefore, the study has external validity for the proposed indication. The safety in children with a weight < 10 kg is unknown because the study investigated subjects with a weight ≥ 10 kg.

Although US CF Foundation (CFF) Patient Registry data indicates that only a small minority of children 2 through 5 years of age will have a weight < 10 kg, it is uncertain whether it also applies to the European population. Based on the 2021 annual report of the European Cystic Fibrosis Society Patient Registry (ECFSPR) it can be assumed that there are underweight children in the range from 2 to 5 years weighing less than 10 kg. Therefore, simulations for subjects weighing 7 kg were performed that demonstrated an

approximately 30% increase of the analytes (with M1-TEZ being approximately 35% greater). Therefore, a lower weight limit of 10 kg is proposed for the dosing recommendations in section 4.2 of the SmPC.

As study 111 is an open-label single-arm trial without a comparator arm, no randomisation or blinding was done. Therefore, only a within-group change from baseline is available.

The improvement (reduction) from baseline in LCI2.5 is smaller than the reduction observed in children 6 through 11 years (-1.71 (95% CI: -2.11, -1.30)). The treatment effect is also smaller than accepted before as clinically relevant. The results of $LCI_{2.5}$ were similar in the two subgroups.

The approved Kaftrio indication in terms of genotype is broad. The optimal age to start Kaftrio in relation to F heterozygotes is still uncertain. This is particularly relevant for F-heterozygotes with less severe CF, for whom no data will become available through ongoing studies. Furthermore, no longitudinal data will become available for subjects with F/MF mutations, although there is less uncertainty for the subjects with severe CF than with less severe regarding the optimal age to start treatment. Consequently, the CHMP requested the MAH to perform a PAES in all children who are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio. It will provide further valuable information regarding the magnitude of effect in the real world that is not already gathered through other studies.

3.4. Unfavourable effects

The following safety findings are observed in Part B unless otherwise indicated.

ELX/TEZ/IVA was generally well tolerated by children 2 through 5 years of age up to 24 weeks. The safety findings 2 through 5 years of age are generally similar to the findings in children 6 through 11 years of age and to adults and adolescents.

The most common AEs ($\geqslant$10% incidence overall) by PT were cough, pyrexia, rhinorrhea, vomiting, COVID-19, nasal congestion, rash, upper respiratory tract infection, decreased appetite, ALT increased, and infective pulmonary exacerbation (PEx) of CF.

SAEs: One SAE of anal and urinary incontinence and abnormal behaviour was possibly related. The other SAE was a not related infective PEx of CF. Overall, the number of SAEs is low, consistent with the finding in children 6 through 11 years of age and lower than in adults and adolescents. There were no deaths.

Related/possibly related AEs and SAEs: The number of related/possibly related AEs and SAEs was 42.7% and 2.7%, respectively. Overall, the related AEs were mostly consistent with the known safety profile of ELX/TEZ/IVA. However, the related AEs aggression, irritability and psychomotor hyperactivity, each 4%, in SOC Psychiatric disorder were observed. This is in line with observation in the population of children 6 through 11 years of age, in which aggression, anxiety and depressed mood, each 1 event (1.5%) were observed.

AESI Elevated transaminase events: 8 (10.7%) subjects had elevated transaminase events, of which 1 (1.3%) led to treatment interruption. Specifically, 8 (10.7%) subjects had ALT increased, and 4 (5.3%) subjects AST increased. The number is similar to the number in subjects 6 through 11 years of age (7 (10.6%)) and to the number in adults and adolescents (22 (10.9%)) in study 102.

The number of ALT increased is similar to the number in subjects 6 through 11 years of age (7 (10.6%)) and to the number in adults and adolescents (20 (9.9.%)) in study 102. The frequency is higher in children 2 through 5 years of age and in children 6 through 11 years of age, therefore, the section 4.8 of the SmPC was amended to reflect the frequency as very common (> 1/10) for ALT increased.

AESI Rash events: in Part A 4 (22.2%) subjects had a total of 6 nonserious rash events, while 15 (20.0%) subjects in Part B. This is generally similar to the subjects 6 through 11 years of age and higher than in the adults and adolescents. However, rash occurs frequently in young children as a symptoms of a common viral disease of the youth.

Discontinuations and disruptions of medication: One subject discontinued due to an SAE of abnormal behaviour. Disruptions occurred in 1 (5.6%) subject in Part A because of unrelated AEs of hyperamylasemia and hyperlipasemia and in 5 (6.7%) subjects in Part B because of the following AEs: 2 subjects with rash, 1 subject with anal and urinary incontinence, 1 subject because of aggression, and 1 subject because of elevation of AEs of ALT, AST, and GGT.

Liver Function Tests: the findings of elevations of liver function test (AST, ALT, bilirubin) are generally in line with the results found in the study in children 6 through 11 years of age and the studies in adults and adolescents. No subjects had total bilirubin >2 × ULN.

3.5. Uncertainties and limitations about unfavourable effects

To be included in part B of Study 111, subjects must have had no elevated serum ALT or AST ≥3 x ULN or total bilirubin ≥2 x ULN at screening and in the previous year; the latter was not an exclusion criterion in the studies in adults or children 6 through 11 years of age. This may have led to the inclusion of healthier subjects. Despite the more stringent exclusion criteria, the incidences of AE of ALT or AST elevations were quite similar, while threshold analyses indicate a trend of more events.

AEs in the SOC Psychiatric disorder (aggression, irritability and psychomotor hyperactivity) appear to be higher in the population of children 2 through 5 years of age, 6 through 11 years of age or compared to adults. Because of the relatively low number of patients in the studies, low incidence of the AEs and the absence of a placebo arm, it is not possible to draw a firm conclusion.

Overall, there is uncertainty on long term safety in children 2 to less than 6 years of age. The open label extension study and PASS planned studies will address this uncertainty. In addition to the two planned PASS studies as aPhV activities in the RMP, monitoring and analysis of the psychiatric-related AEs in the PSURs for all age groups will be presented in 3 age categories.

3.6. Effects Table

Table 23: Effects Table for Kaftrio granules in a combination regimen with ivacaftor for the treatment of CF in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the CFTR gene.

Effect	Short Description	Unit	Treatment ELX/TEZ/IVA	Control -	Uncertainties/ Strength of evidence	References
Favourable Effects						
SwCl	Change 0-24 wks LS mean (95% CI) from baseline	Mmol/l	-57.9 (-61.3, -54.6)	-	**Unc**: open-label, single-arm trial	Study 111
LCI2.5	Change 0-24 wks LS mean (95% CI) from baseline	number	-0.83 (-1.02, -0.66)		**Unc**: open-label, single-arm trial	Study 111
PEx	Event rate/year	number	0.32	-	**Unc**: open-label, single-arm trial **Unc**: 24 week trial	Study 111
Unfavourable Effects						
Elevated Transaminase Events	Events of increased transaminases (Part B)	%	10.7%	-	**Unc**: Open-label, single arm study,	Study 111
Rash	Events (Part B)	%	20.0%	-	**Unc**: Open-label, single arm study	Study 111

Abbreviations: SwCl = sweat chloride, $LCI_{2.5}$ = number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, PEx = pulmonary exacerbation

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Previously developed popPK models that described the PK of ELX, TEZ, and IVA in CF adults, adolescents, 6-11y subjects were used to establish the exposure of ELX, TEZ, and IVA in children aged 2-5 years. Overall, it can be concluded that in subjects 2 through 5 years of age, the majority of ELX, TEZ, and IVA exposures were within the exposure range observed for subjects ≥18 years of age for each weight group.

The LS mean absolute change from baseline through Week 24 in SwCl is well above the CHMP accepted minimal improvement of approximately 10 mmol/l to be considered as clinically relevant.

The LS mean absolute change in LCI2.5 from baseline through Week 24 of -0.83 is small and doubtfully clinically relevant as it is just below the natural variability.

Strength of the evidence

In CF, sweat chloride is increased, and a decrease can be considered as an effect on the underlying pathology. Therefore, the observed reduction in sweat chloride is an important parameter for measuring the pharmacodynamic effect. Besides the decline of lung function, pulmonary exacerbations impact survival in cystic fibrosis and reduce health-related quality of life. Preservation of lung function alongside reductions in the rate of pulmonary exacerbations are the main goals of the treatment of cystic fibrosis. The observed reductions of SwCl and LCI are supported by all exploratory parameters, i.e. growth parameters and markers of pancreatic function and inflammation.

Observed improvements in ppFEV1 and SwCl in children 2 to 5 years of age were consistent with previous results in children 6 through 11 years old and in adults and adolescent populations.

Impact of the uncertainties

As study 111 is an open-label single-arm trial without a comparator arm, no randomisation or blinding was done. Therefore, only a within-group change from baseline is available.

Based on the 2021 annual report of the European Cystic Fibrosis Society Patient Registry (ECFSPR) it can be assumed that there are underweight children in the range from 2 to 5 years weighing less than 10 kg. Therefore, a lower weight limit for children weighting less than 10 kgs was implemented in the dosing recommendations.

The LCI2.5 can measure changes in the small airways. In CF, the small airways are affected earlier than the large airways. Therefore, the use of the LCI2.5 as a measurement of efficacy is sensitive, given the more preserved lung function in children than in adults. The improvement (reduction) from baseline In LCI2.5 is smaller than the reduction observed in children 6 through 11 years and below the accepted limit as being clinically relevant. However, lung function in young children is better preserved than in children 6 through 11 years of age. Therefore, a slightly lower benefit is not unexpected. Therefore, the results are doubtfully clinically relevant.

The optimal age to start Kaftrio in relation to certain F heterozygotes is still uncertain. In that light, the collection of efficacy data post-approval for children that are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio needs to be further explored post approval. Consequently the CHMP requested the MAH to perform, a PAES in all children who are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio. It will provide further valuable information regarding the magnitude of effect in the real world that is not already gathered through other studies.

Safety

There is uncertainty regarding the relevance of the effects observed in juvenile rats, particularly convulsions and lethality seen at doses of 4-fold human exposure.

ELX/TEZ/IVA was generally well tolerated by children 2 through 5 years of age up to 24 weeks, as shown by the reported low number of serious adverse events, treatment interruptions and treatment discontinuations due to AE.

Impact of the uncertainties

To be included in part B of Study 111, the exclusion criteria for the hepatic function test were stricter, which may have led to the inclusion of healthier subjects. Nevertheless, the incidences of AE of ALT or AST elevations were quite similar, but the threshold analyses indicate a trend of more events. However, this is not considered worrisome because elevations of ALT and AST are more common in children compared to adults.

The relevance of the observation of the related AEs in SOC Psychiatric disorder is unclear. This frequency is in line with observation in children 6 through 11 years of age but higher compared to the adults and adolescents population. As the limited clinical data do not allow for a firm conclusion, psychiatric disorders will be monitored post-marketing.

3.7.2. Balance of benefits and risks

In this procedure, the extension of the indication to children 2 through 5 years old is based on the principle of partial extrapolation from adults and adolescents to paediatric patients. The extension must be supported by comparable PK exposures, acceptable safety, and a similar PD/efficacy effect.

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations of clinical data from subjects 2 through 5 years of age, subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 14 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 2 through 5 years of age.

In study 111 in CF patients 2 through 5 years of age, efficacy was a secondary objective. Clinically relevant improvements were found in the changes from baseline for the SwCl. These improvements were consistent with previous results in subjects 6 through 11 years of age adults and adolescent populations, confirming the justification of partial extrapolation. Other endpoints were supportive of the finding in SwCl.

ELX/TEZ/IVA was generally well tolerated by children 2 through 5 years of age up to 24 weeks, as shown by the reported low number of serious adverse events, treatment interruptions and treatment discontinuations due to AE. No new important risks were identified. Hepatotoxicity is already identified as an important potential risk.

The earlier introduction of modulator therapy in younger patients from 2 years of age might be beneficial, as this modulator therapy has the potential to prevent the detrimental effects of CF. Considering these paediatric patients are treated in specialized clinics and frequently monitored, some more severe safety concerns, such as hepatotoxicity, are considered acceptable and manageable in clinical practice. In addition, the safety will be further substantiated in the follow-up extension study.

The optimal age to start Kaftrio in relation to certain F heterozygotes is still uncertain. In that light, the collection of efficacy data post-approval for children that are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio needs to be further explored post approval. Consequently the CHMP requested the MAH to perform a PAES in all children who are F heterozygotes (aged 2-5 years) who will receive treatment with Kaftrio. It will provide further valuable information regarding the magnitude of effect in the real world that is not already gathered through other studies.

3.8. Conclusions

The overall benefit/risk balance of Kaftrio is positive, subject to the conditions stated in section 'Recommendations'

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kaftrio is not similar to Symkevi and Tobi Podhaler within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Kaftrio new pharmaceutical form (granules) is favourable in the following indication:

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see section 5.1).

The CHMP therefore recommends the extension of the marketing authorisation for Kaftrio subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post Authorisation Efficacy Study (PAES): Post-authorisation efficacy In order to further characterise the long-term efficacy among children with CF who are heterozygous for *F508del* and aged 2 through 5 years, the MAH should conduct and submit the results of a long-term effectiveness registry-based study comparing disease progression among children with CF who are heterozygous for F508del-CFTR and are aged 2 through 5 years at the time of Kaftrio treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kaftrio treatment, in addition to a longitudinal historical cohort, according to an agreed protocol	Full protocol submission by June 24 Enrolment completed by Dec 2024 Final report Due date 31 Dec 2029

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0265/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.