11 November 2021
EMA/713972/2021
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/0008/G

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATC	anatomic class
BP	blood pressure
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CM	Continuous Manufacturing
Cmax	maximum concentration
CPAP	clinical pharmacology analysis plan
CPP	Critical process parameter
CPV	Continuous Process Verification
CQA	Critical Quality Attribute
CRF	case report form
CSR	clinical study report
Ctrough	predose concentration
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DLR	Development and Launch Rig
DNA	deoxyribonucleic acid
DoE	Design of experiments
ECG	Electrocardiogram
EDC	electronic data capture
EG	extragranular
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F508*del*	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FDA	Food and Drug Administration
FDC	fixed dose combination
F/F	homozygous for F508*del*
F/MF	heterozygous for F508*del* and a CFTR minimal function mutation
FAS	Full Analysis Set
FDC	fixed-dose combination
FE-1	fecal elastase-1
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
HPLC	High performance liquid chromatography
HR	heart rate
IDMC	independent data monitoring committee
IEC	independent ethics committee
ICF	informed consent form
ICH	International Council for Harmonisation
IG	intragranular

IPC	In-process control
IPD	important protocol deviation
IRB	institutional review board
IR	Infrared
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
IXRS	interactive voice/web response system
IWRS	interactive web response system
KF	Karl Fischer titration
LCI	lung clearance index
LCI2.5	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LCI5.0	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value
LFT	liver function test
LS	least squares
LUM	lumacaftor
M1-IVA	metabolite of IVA
M1-TEZ	metabolite of TEZ
M23-ELX	metabolite of ELX
max	maximum value
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function (mutation)
min	minimum value
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size
NOR	Normal Operating Range
NOS	not otherwise specified
OATP	organic anion transporting polypeptide
OE	ophthalmologic examination
P	probability
PACMP	post-approval change management protocol
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbation, pulmonary exacerbations
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetic, pharmacokinetics
PK	Product Key
PN	preferred name
PR	PR interval, segment
PLS-LDA	partial least squares-linear discriminant analysis
PPQ	Process Performance Qualification
PT	Preferred Term
ppFEV1	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
qd	once daily
QbD	Quality by design
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RH	Relative Humidity
RNA	ribonucleic acid
RR	interval from the onset of 1 QRS complex to the next; use R-R if using with "intervals," i.e., "R-R interval"
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error

SI	SI units (International System of Units)
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	standard operating procedure
SwCl	sweat chloride
TAMC	Total Aerobic Microbial Count
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
TYMC	Total Combined Yeasts/Moulds Count
ULN	upper limit of normal
US/USA	United States/United States of America
USP/NF	United States Pharmacopoeia/National Formulary
VMP	Validation Master Plan
WHO-DD	World Health Organization-Drug Dictionary

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Ireland) Limited submitted on 8 March 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new strength of 37.5 mg/25 mg/50 mg film-coated tablets. grouped with a type II variation (C.I.6.a) to include paediatric use (6 to 11 years).

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Kaftrio was designated as an orphan medicinal product EU/3/18/2116 on 14 December 2018 in the treatment of cystic fibrosis (CF).

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 <insert link>

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0397/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0397/2020 covering the application was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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.

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

The application was received by the EMA on	8 March 2021
The procedure started on	25 March 2021
The Rapporteur's first Assessment Report was circulated to all CHMP members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 July 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 August 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	15 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 September 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	14 October 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	19 October 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 October 2021
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	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication reads as follows: Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation (see section 5.1).

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 aiding in the regulation of 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 the individuals in the US and 81.1% of the individuals in Europe).

2.1.2. Epidemiology and screening tools

CF affects approximately a total of 31,000 individuals in the US and a total of 42.000 in the EU (excluding the data from Russia, Turkey and Israel)[1],[2]. 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 Europe, the median age of all CF patients is 18.5 years (with the youngest patient being diagnosed just after birth and the oldest patients being 88.4 years of age). Despite advances in treatment, the current median age of death in a patient with CF was approximately 31 years in 2018, and the future predicted median age of survival is approximately 47 years[1,2].

2.1.3. 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, that is responsible for aiding in the regulation of salt and water absorption and secretion. More than 2000 mutations in the *CFTR* gene have been identified.

CFTR mutations can be classified according to the mechanisms by which they disrupt CFTR function.

[1] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2019.
[2] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019.

• 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 a 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 these 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 transport 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).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

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[2]. 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 take into account 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 ≥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[3].

2.1.5. 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. 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 substantial benefit derived from the robust 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 F*508del* 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 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

[3] Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 181S:S4.

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 age 12 years and older with cystic fibrosis (CF) who have at least one *F508del*-mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*)-gene.

Initially, the applicant applied for an extension to children aged 6 years and older. At the time of the initial application, the indication was as follows (the applicant's proposed changes to the indication are shown in bold and strikethrough):

*Kaftrio is indicated in a combination regimen with ivacaftor ~~150 mg tablets~~ for the treatment of cystic fibrosis (CF) in patients aged **6**~~12~~ years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation (see section 5.1).*

With the approval of extension of indication II/001 on 26 April 2021 Kaftrio became indicated "in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene (see section 5.1)." This indication is referred as the "F/Any" indication from 12 years onwards.

In view of this recent approval of the F/Any indication from 12 years onwards, the applicant requested an amended indication i.e. *Kaftrio is 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 (see section 5.1).*

The age-adapted ELX/TEZ/IVA combinations therapy is dosed orally each day in 2 tablets as follows:

Dosing recommendation for patients aged 6 years and older		
Age (weight)	**Morning Dose**	**Evening Dose**
6 to <12 years (weighing <30 kg)	Two tablets, each containing ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg	One tablet containing ivacaftor 75 mg
6 to <12 years (weighing ⩾30 kg)	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg
⩾12 years	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg

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 that contain fat are those prepared with butter or oils or those containing 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 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).

2.3. Quality aspects

2.3.1. Introduction

This application concerns a line-extension to add a new film-coated tablet strength of elexacaftor 50 mg, tezacaftor 25 mg, ivacaftor 37.5 mg to the already authorised Kaftrio (elexacaftor 100 mg, tezacaftor 50 mg, ivacaftor 75 mg) film-coated tablets. This line extension is submitted together with a type II variation to extend the indication to children aged 6-11 years.

Other ingredients of the tablets are:

Tablet core: hypromellose (E464), hypromellose acetate succinate, sodium laurilsulfate (E487), croscarmellose sodium (E468), microcrystalline cellulose (E460(i)), magnesium stearate (E470b)

Tablet film coat: hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), iron oxide red (E172)

The product is packed in a blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper backed aluminium foil lidding as described in section 6.5 of the SmPC.

2.3.2. Active Substance

No module 3.2.S has been submitted within this line extension.

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is an immediate-release film-coated tablet for oral administration. The tablet is a fixed-dose combination (FDC) of the active ingredients elexacaftor, tezacaftor and ivacaftor.

As indicated above, the FDC tablet strength introduced with this line extension contains 50 mg of elexacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor. It is a light orange film-coated tablet, debossed with "T50" on one face and plain on the other face. The approximate dimensions are 6.4 mm x 12.2 mm.

The elexacaftor/tezacaftor/ivacaftor 50/25/37.5 mg tablets contain the same excipients as the existing tablet strength.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except iron oxide yellow and iron oxide red, which comply with EC Regulation 231/2012. 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 all components of the FDC tablet was demonstrated with an open dish stability study at 40ºC /75% RH for 6 months.

The formulation development was mainly based on the authorised 100/50/75 mg strength. The 50/25/37.5 mg tablet uses the same core tablet blend as the 100/50/75 mg strength and the tablet weight is adjusted to achieve the desired dose. The tablet is coated with a light orange, non-functional film coat containing the same components as the film coat used for the elexacaftor/tezacaftor/ivacaftor 100/50/75 mg tablet.

A detailed discussion on the age-appropriateness of the finished product for use in children of 6 through 11 years has not been provided in the quality part of the dossier. No direct safety issues are foreseen concerning the excipients and their quantities in the formulation for use in children. All excipients have been used previously in the intended age group (such as the Symkevi tablet for pediatric populations 6-11 years of age). According to the drug acceptability data provided in module 5, most children were able to swallow the tablets. The dimensions of the tablets fulfil the requirement of the PIP (maximum dimension of 14 mm).

The proposed dissolution methods for elexacaftor, tezacaftor and ivacaftor are the same as per authorised 100/50/75 mg tablets. In general, they have been shown to be suitable for the 50/25/37.5 mg strength as well. Extensive (multivariate) studies have been carried out to demonstrate the discriminatory power of the three methods including data on the statistical significance of the studied process parameters and/or material attributes. The discriminatory power of the routine dissolution methods has been further substantiated by a batch with a core hardness above the IPC limit which does not meet the acceptance criterion for routine dissolution testing of the three active substances. Keeping in mind that the proposed dissolution methods have been previously approved for the 100/50/75 mg strength, the provided data on the discriminatory nature of the methods is considered sufficient.

The manufacturing process development section is largely identical to that of the authorised 100/50/75 mg strength. The manufacture of the FDC tablets uses a continuous manufacturing (CM) process, starting with the introduction of formulation components and ending with film-coated tablets. The FDC product was developed using dry granulation on Vertex's CM platform known as the Development and Launch Rig (DLR). This section comprises an overview of the applied CM process, operational considerations such as segregation points and residence times of product keys in specific sections of the equipment train allowing the removal of a sufficient number of adjacent product keys in case of non-conformance, process controls including the final blend potency NIR method, the Quality by Design (QbD) approach and the design space development.

All principles of CM (for the stages intragranular blending, extragranular blending, compression, and film-coating) have been explained in the dossier. The general approach is described, providing a high-level process schematic and narrative. The proposed process is a hybrid process, with the majority of integrated unit operations being run in continuous mode, with batch mode start (initial mixing) and finish (primary packaging). The registration batches were manufactured at a batch size of 60 kg using the continuous process. In the continuous process, material is tracked using the Product Key (PK) concept. The PK is the smallest unit of material that can be segregated and has been defined. It is explained that specific PKs having in-process controls (IPC) results outside the acceptance criteria will be removed from the process; there are two 2 segregation points in the continuous process, allowing for removal of non-conforming PKs. Specific aspects of the process are discussed in more detail, including process and equipment design considerations, feedback loops, segregation points, etc. The loss-in-weight feeders, blenders, roller compactor, tablet press and tablet coaters are critical to product quality. Specific operational considerations are also discussed: start-up, shut-down and segregation approach.

The CM process control strategy consists of 4 levels, each of which are discussed: unit operation control(s) to set point(s), design space monitoring, IPC and product specification. Automated feedback loops are used to drive each unit operation towards manufacturing set-points. Process parameters and design space limits are monitored in real-time, and any excursions are detected and alerted in real-time. In-process controls and limits are defined, as is the finished product specification.

A key part of the control strategy is the 'typical final blend potency' IPC method, which consists of two parts: LIW feeder data and a NIR method to control homogeneity and potency of the blend prior to

compression. The model used in the NIR method is a PLS-LDA model used qualitatively. The NIR model principles, development and validation, maintenance and life-cycle management are all discussed. The model is critical to product quality and is considered a high-impact model. The NIR method was developed for the authorised 100/50/75 mg strength and was extensively discussed during the marketing authorisation application of the authorised 100/50/75 mg strength. The same blend is used for the proposed 50/25/37.5 mg strength and the dossier of the proposed 50/25/37.5 mg strength is largely in line with the outcome of the discussions for the authorised 100/50/75 mg strength. A post-approval change management protocol (PACMP) has been proposed to manage changes of the NIR model. This PACMP is in line with the *EMA Addendum* to *EMA/CHMP/CVMP/QWP/17760/2009 Rev 2: Defining the Scope of a NIRS Procedure*.

The manufacturing process development initiated with a material risk assessment. Experimental designs were conducted in a multivariate manner for the granulation and compression unit operations. Separately, a unit-operation specific experiment was conducted for the film coating process.

After the criticality assessment, the design space was defined.

Differences in the outcomes of the DoE studies, as well as the resulting differences in the design space, fixed parameters and IPC limits between the 100/50/75 mg and the 50/25/37.5 mg tablets have adequately been discussed by the applicant. The main reason for the differences in the outcome of the DoE appears to be the narrower desired manufacturing range for the compression force of the lower strength. The other differences are explained by different settings of the line rate, spray rate, and spray time.

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 container closure system for the FDC tablets is the same as used for the 100/50/75 mg strength. It consists of a thermoform blister consisting of a clear Aclar (PCTFE – polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil lidding. The Aclar/foil blister configuration will be placed into an appropriate secondary container. All packaging components are suitable for their intended use and comply with Commission Regulation (EU) No 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by Vertex Pharmaceuticals Incorporated.

The intended commercial batch size and the commercial line rate have been defined As in the existing tablet strength, both tezacaftor and ivacaftor active substances are incorporated into the FDC tablet formulation as amorphous spray-dried dispersion (SDD), whereas elexacaftor is incorporated as a crystalline solid.

The manufacturing process starts with the intra-granular (IG) blending of the excipients in a batch mode, followed by the continuous manufacturing process which comprises: feeding and IG blending of the actives and IG excipients; dry granulation and milling; extra-granular (EG) blending of granules and EG excipients; compression, and coating (which can also be performed in an offline mode). The primary packaging is subsequently conducted on a batch mode.

The process is considered to be a non-standard manufacturing process.

A flow diagram depicting the CM part including segregation points as well as critical process parameters, process parameters, and in-process controls has been provided. A schematic of the DLR configured for dry granulation has also been provided, outlining equipment types and testing points The manufacturing process has been described in sufficient detail. Design space limits are as per those defined in the manufacturing process development section and the ranges stated are as per evaluated desired manufacturing ranges. Process parameter set points represent those studied or fixed during development. Coating can be carried out in an online or offline mode. The same sequence and process parameters are used for both modes. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space, NOR and set points.

Comprehensive information is provided regarding process controls. The summary of critical process parameters (CPPs), PP and IPCs is in line with that presented in the manufacturing process development section. IPC methods are discussed, as are mass flow and the NIR method. The NIR method is a qualitative method, used to discriminate between samples inside and outside the limits of the range (95 and 105%). This range reflects the proposed assay in the finished product specification. The model justification is extensive and is intended to ensure that adequate variability is incorporated. The content uniformity method defined in 3.2.P.5.2 of the eCTD is used for reference analyses. Model validation considers ICH Q2 and the EU NIR Guidelines. The model is considered high impact, directly affecting product quality.

A continuous process verification (CPV) approach to validation has been implemented for the 50 mg elexacaftor / 25 mg tezacaftor / 37.5 mg ivacaftor FDC tablet. A The DLR is a highly automated CM line that will be used for commercial manufacture. A comparison between clinical batches manufacturing details and the one used for routine commercial manufacture has been presented. Process performance understanding is further supported by conducting development (QbD) experiments on the same continuous manufacturing line (DLR) and by using multivariate analysis to link process parameters to product CQAs and to define design spaces within which product quality is assured. Process parameter and IPC data are collected and reported continuously throughout manufacture, both for the purpose of process monitoring and control. Process capability has been demonstrated through the analysis of in-process control variability, which has informed the sampling plan and frequency, as well as through the analysis of process parameter variability, which has demonstrated the ability of the process to operate within design space limits. Furthermore, there is a thorough understanding of product quality during start-up and shutdown, as well as before and after pauses. The residence time distribution on the DLR has been characterised; procedures are in place to allow segregation of all potentially impacted material. The high level of process understanding obtained from development work and clinical manufacture experience on the DLR, together with the high level of process interrogation during each batch, justifies completion of process performance qualification (i.e. process validation via continuous process verification) via manufacture of two commercially representative batches. Successful completion of these batches according to the requirements in the (VMP) will conclude PPQ. Commercial manufacture will continue following an assessment of the PPQ batches.

Overall, it has 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.

As indicated above, a post-approval change management protocol (PACMP) has been proposed to manage changes of the models used for IPC of the Kaftrio FDC tablets during the lifecycle of the product. All model updates will be managed in line with EMEA/CHMP/CVMP/QWP/17760/2009 Rev2, *Guideline on the use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations*. This is acceptable.

In the original submission, a second PACMP to manage changes of the finished product design space and addition of manufacturing sites was proposed. In line with the outcome of the application for the 100/50/75 mg strength, this second PACMP has been withdrawn.

Product specification

The finished product release specifications are appropriate tests for this kind of dosage form: appearance, identification (IR), assay of each of the active substances (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution of each of the active substances (HPLC), water content (KF) and microbial limits (TAMC, TYMC, *E. coli*).

The proposed finished product specification is identical to that of the authorised 100/50/75 mg strength, with the only difference in the tablet debossing and tablet coating colour.

Acceptable justifications have been provided for omitting tests for the physical form, chiral purity, residual solvents, elemental impurities, and nitrosamines in the finished product specification. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. using both the Option 1 and Option 2b approach, concluding that all Class 1 and Class 2A elemental impurities in the tablets will be consistently below 30% of the established PDEs and no additional controls are required. This is in line with the conclusions for the authorised 100 mg/50 mg/75 mg product and considered sufficient. Confirmatory testing of representative batches including three commercial elexacaftor active substance batches, ten commercial tezacaftor active substance batches, nine commercial ivacaftor active substance batches, four commercial tezacaftor SDD batches, and four commercial ivacaftor SDD batches confirmed that the content of Class 1 and Class 2A elemental impurities is consistently below 30% of the ICH Q3D (R1) Option 1 limits. The content of Class 1 and Class 2A elemental impurities were also shown to be below 30% of the ICH Q3D (R1) Option 1 limits for all tablet excipients with the exception of Opadry Orange film coating system. For Opadry Orange, the Option 2b summation approach was employed to demonstrate that the maximum daily intake of each elemental impurity is well below 30% of its respective permitted daily exposure. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) 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 no risk was identified on the possible presence of nitrosamine impurities in the active substances or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods are identical to those used for the 100/50/75 mg strength. The methods have been adequately described and validated. Reference standards have been sufficiently described.

Batch analysis results have been provided for four batches used in the clinical studies with a batch size of 60 kg. The results demonstrate compliance with the release specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored at 25°C/60% RH (12 months), 30°C/75% RH (12 months), and 40°C/75% RH (six months) according to the ICH guidelines were provided. The batches of Kaftrio are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, HPLC assay (three actives), HPLC degradation products, chiral purity, dissolution (three actives), XRPD physical form (1. elexacaftor; 2. tezacaftor and 3. ivacaftor), KF water content, water activity, and microbiological quality (TAMC, TYMC, *E.coli*). The analytical procedures used are stability indicating.

No significant changes or trends have been identified at any storage condition.

Photostability of one 50/25/37.5 mg commercial scalebatch was evaluated per ICH Q1B Option 2. Tablets and covered control samples were exposed at not less than the ICH minimum for UV (320 – 400nm) and visible (400 – 800nm) light. Samples were tested for appearance, assay, degradation products and chiral purity. No changes were observed in the exposed tablet samples as compared to the covered control, confirming that Kaftrio FDC tablets do not require light protective packaging.

Forced degradation studies have not been separately performed for the 50/25/37.5 mg product, but only for the 100/50/75 mg product. The results of these studies are considered representative for the 50/25/37.5 mg tablets.

Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. Magnesium stearate is of vegetable origin.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The development of the 50/25/37.5 mg tablets to treat children aged 6-11 years, is largely based on the already authorised Kaftrio 100/50/75 mg film-coated tablets. For instance, the same blend and associated continuous manufacturing process and process controls are used for the core tablets. The applicant has applied QbD principles in the development of the finished product and its manufacturing process. A design space has been proposed for the granulation and compression step.

Critical aspects identified during the marketing authorisation application for the authorised strength such as the use of a single qualitative NIR PAT method to check the final blend potency prior to compression and the ability of this method to correctly identify product keys exceeding the typical potency have been addressed in the dossier of the line extension in line with the outcome of the objections raised on the authorised strength. Moreover, the same finished product specification, container closure system, and shelf life are applied for the line extension. No major quality objections have been identified for the line extension.

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.

2.3.5. 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.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

No new non-clinical studies have been submitted for this procedure, which is agreed by CHMP.

2.4.1. Ecotoxicity/environmental risk assessment

Table 1 ***Summary of main study results***

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		µg/L	> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)			(Y/N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =	List all values

Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**valu e**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

2.4.2. Discussion on non-clinical aspects

The MAH did not submit new non-clinical data which is acceptable. The new indication in children from 6 years to 12 years will not affect conclusions on the environmental risk of Kaftrio active substance to the environment.

Current available non-clinical data support the use in the children population from 6 to 12 years of age and in patients with F/any mutation.

2.4.3. Conclusion on the non-clinical aspects

Available non-clinical data support the use in the extension of the indication in children from 6 to 12 years of age, with F/any mutation.

2.5. Clinical aspects

2.5.1. Introduction

GCP

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.

- **Tabular overview of clinical studies**

Table 2 Overview of clinical studies submitted

Study number	design	patients	duration	Primary objectives	Phase
VX18-445-106 Part A	Open-label	16 CF patients 6 through eleven years of age	15 days	Evaluation of the pharmacokinetics,	completed
VX18-445-106 Part B	Open-label	66 CF patients 6 through eleven years of age	24 weeks	Evaluation of the safety and tolerability	completed
VX19-445-107	Open-label	CF patients from parent study VX18-445-106 Part B 6 years of age and older	96 weeks	Evaluation of the long-term safety and tolerability	ongoing

2.5.2. Pharmacokinetics

In support of the current line extension, Phase 3 Study 106 in paediatric CF patients was conducted to evaluate the PK of ELX, TEZ, and IVA administered in triple combination in subjects 6 through 11 years of age, and to assess if target exposures observed in subjects ≥18 years of age were achieved in the younger population with the proposed dosing scheme.

For patients 6 through 11 years of age, ELX/TEZ/IVA is proposed to be administered with fat-containing food as follows:

- Patients weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h
- Patients weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h

Based on the provided Study 106, in subjects 6 through 11 years of age, it was shown that applying a 30 kg cut-off for the applied normal adult for 50% of the adult dose would result in ELX, TEZ, and IVA exposures most similar to exposures in subjects ≥18 years of age while maintaining M23-ELX and M1-TEZ exposures generally within ranges seen in previous studies of ELX/TEZ/IVA and TEZ/IVA (Table 3).

Further simulation showed that, when applying a 30 kg cut-off, the majority of ELX, TEZ, and IVA exposures for the <30 kg and ≥30 kg weight group were within the exposure range for subjects ≥18 years of age. Exposures for subjects 6 through 11 years of age who weighed ≥30 kg were on the higher end of the exposure range for subjects ≥18 years of age, whereas exposures for subjects who weighed <30 kg were on the lower end of the exposure range (Figure 2).

The cut-off weight in paediatric patients (30 kg) for Kaftrio is identical to that for Symkevi (tezacaftor/ivacaftor).

Although the range of M23-ELX and M1-TEZ exposures in paediatric patients 6 through 11 years of age weighing ≥30 kg is somewhat increased as compared to the exposure range in adults and adolescents, the exposures of these metabolites are within the range of prior clinical experience.

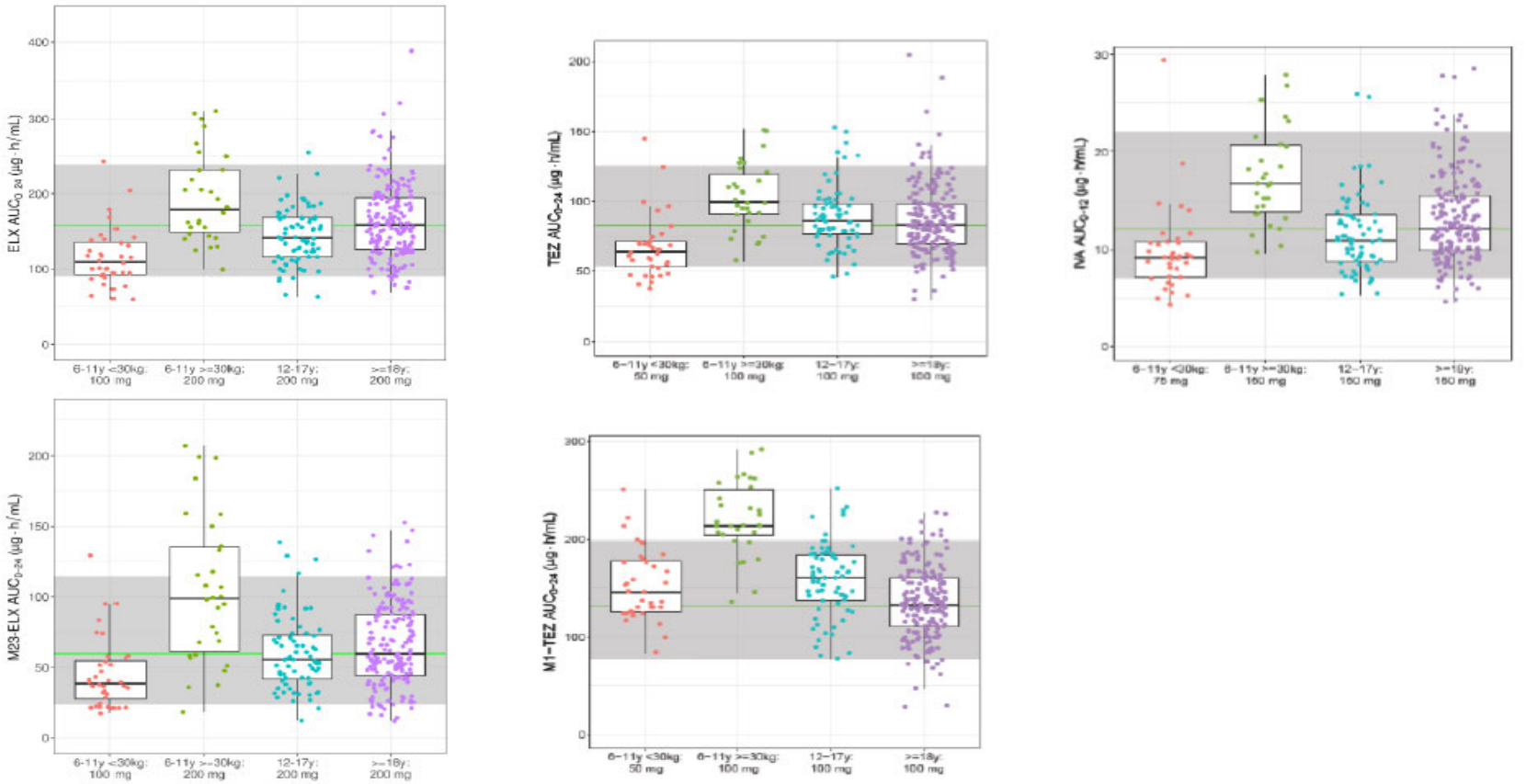
In the SmPC section 5.2, PK data for ELX, TEZ and IVA and for active metabolites M23-ELX and M1-TEZ are presented.

Table 3 Summary of ELX, M23-ELX, TEZ, M1-TEZ, and IVA observed steady-state AUC by age group, 30-kg weight cut-off (popPK Studies Q075 and Q076)

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
6 through 11 years	*(Both doses combined)*	66	152 (63.2)	60, 310	66	71.9 (49.1)	17.4, 207	66	83.4 (29.1)	37.4, 151	66	183 (50.0)	83.8, 291	66	13.3 (6.09)	4.23, 29.4
<30 kg	100 mg qd/ 50 mg qd/ 75 mg q12h	36	116 (39.4)	60, 243	36	45.4 (25.2)	17.4, 129	36	67.0 (22.3)	37.4, 145	36	153 (36.5)	83.8, 250	36	9.78 (4.50)	4.23, 29.4
≥30 kg	200 mg qd/ 100 mg qd/ 150 mg q12h	30	195 (59.4)	99.4, 310	30	104 (52)	18.3, 207	30	103 (23.7)	57.7, 151	30	220 (37.5)	135, 291	30	17.5 (4.97)	9.62, 27.9
12 through 17 years	200 mg qd/ 100 mg qd/ 150 mg q12h	72	144 (37.5)	63.3, 255	72	60.1 (26.3)	12.2, 139	69	88.9 (22.4)	46.1, 152	69	157 (37.3)	77.2, 252	69	11.6 (4.05)	5.28, 26.0
≥18 years	200 mg qd/ 100 mg qd/ 150 mg q12h	179	163 (50.6)	68.9, 389	179	65.7 (29.6)	12, 153	186	86.4 (24.8)	30.1, 204	186	134 (36.8)	27.8, 227	186	13.1 (4.58)	4.57, 28.6

Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31
ELX: elexacaftor; IVA: ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Figure 1. Summary of steady-state AUC by age group for ELX, TEZ, IVA, and metabolites (popPK Studies Q075 and Q076)



Source: Module 5.3.3.5/Report Q075/Figure 7-12, Module 5.3.3.5/Report Q076/Figure 43, Figure 98, and Figure 153
EBE: empirical Bayes estimate; ELX: elexacaftor; IQR: interquartile range; IVA: ivacaftor; TEZ: tezacaftor; y: years of age
Notes: Green horizontal line represents the median of the adult values, and the gray shaded area indicates the 5th and 95th percentiles of the adult values. Boxplots: median is represented by a horizontal line, and the IQR is represented by a box. The whiskers mark the largest and smallest values within 1.5 × IQR. Dots represent individual EBE values.

In this paediatric application, a lower dose Kaftrio tablet is included (i.e., ELX 50/TEZ 25/IVA 37.5 mg FDC tablet as compared to the 'adult' ELX 100/TEZ 50/IVA 75 mg FDC tablet). In comparative bioavailability Study 011, exposures of ELX, TEZ, and IVA were unchanged in terms of AUC0-inf or Cmax when the study drug was administered as 2 low-dose ELX 50/TEZ 25/IVA 37.5 mg FDC tablets or 1 ELX 100/TEZ 50/IVA 75 mg reference tablet.

2.5.3. Pharmacodynamics

There are no new pharmacodynamic studies submitted. However, the pharmacological parameter sweat chloride (SwCl) was studied in the main pivotal study; the results are presented and discussed in below sections of this report (see clinical section).

2.5.4. Discussion on clinical pharmacology

In support of the current line extension, Phase 3 Study 106 in paediatric CF patients was conducted in order to evaluate the PK of ELX, TEZ, and IVA administered in triple combination in subjects 6 through 11 years of age, and to assess if target exposures observed in subjects ≥18 years of age were achieved in the younger population with the proposed dosing scheme.

For patients 6 through 11 years of age, ELX/TEZ/IVA is proposed to be administered with fat-containing food as follows:

- Patients weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h
- Patients weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h

The results of Study 106 demonstrated that for subjects 6 through 11 years of age the distributions of individual ELX, TEZ, and IVA exposures were within the range of those observed in subjects ≥18 years of age. Further, the M23-ELX exposures were within the clinical experience of ELX/TEZ/IVA, and M1-TEZ exposures were generally consistent with the expected clinical experience of ELX/TEZ/IVA and TEZ/IVA.

In conclusion, updated PK data for ELX, TEZ and IVA and for the M23-ELX and M1-TEZ metabolites reflecting clinical activity have been included in the SmPC section 5.2 as requested and agreed by CHMP.

2.5.5. Conclusions on clinical pharmacology

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

2.6. Clinical efficacy

2.6.1. Dose-response studies and main clinical studies

No dose-response studies in children 6-12 years are submitted.

2.6.2. Main study

Title of Study : A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age (study VX18-445-106)

Methods

Figure 3 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

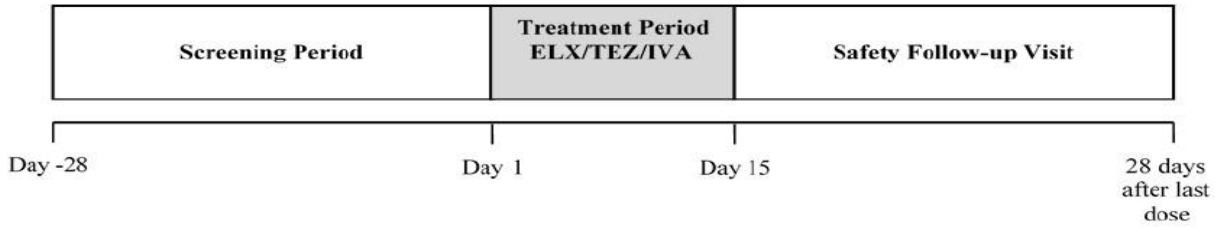
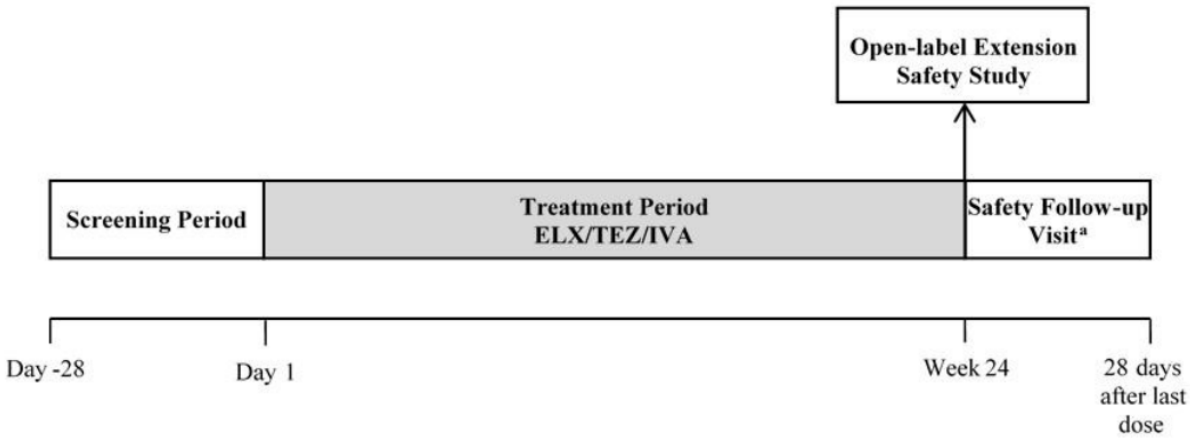


Figure 4 shows the study design of part B.

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 (enrolment was based on the eligibility criteria specified within the Open-label Extension Safety Study protocol).

Figure 3 Part B Study Design



The Safety Follow-up Visit was scheduled to occur 4 weeks (± 7 days) after the last dose. This visit was not required for subjects who enrolled in an optional open-label extension safety study within 28 days of the last dose.

Study Participants

The in- and exclusion criteria were identical for parts A and part B

Main Inclusion criteria

- Subject (or his or her legally appointed and authorized representative) signed and dated an ICF, and an assent form.

- Subjects (males and/or females), 6 through 11 years of age, inclusive, on the date of informed consent.
- Subjects who weighed ≥ 15 kg without shoes at the Screening Visit.
- Confirmed diagnosis of CF as determined by the investigator.
- 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). Genotype was confirmed at the Screening Visit.
- Subjects with FEV1 ≥40% of predicted normal for age, sex, and height using equations of the Global Lung Function Initiative (GLI) at the Screening Visit. Spirometry measurements must have met American Thoracic Society/European Respiratory Society criteria for acceptability and repeatability.
- Subjects with stable CF disease at the start of the Treatment Period as deemed by the investigator.
- Female subjects had a negative serum pregnancy test at the Screening Visit.
- Subjects of childbearing potential and who were sexually active met the contraception requirements

Main Exclusion criteria

- History of any illness or any clinical condition that, in the opinion of the investigator, could confound 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.
    - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
    - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).
- Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
- Any of the following abnormal laboratory values at screening:
    - Haemoglobin <10 g/dL
    - Total bilirubin ≥2 × upper limit of normal (ULN)
    - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN

Treatments

Part A

The ELX dose of 100 mg qd selected for evaluation in Part A was determined based on population-PK modelling utilizing data from adults and simulating exposures over a range of body weights typical for

a population of 6- to <12-year-olds, ranging from 15 to 50 kg. Based on the simulations, an ELX dose of 100 mg qd was predicted to provide exposures that would not exceed the exposures observed in adults dosed with 200 mg qd. Hence, the ELX 100-mg qd dose was predicted to be safe and was evaluated in Part A for all subject weight groups.

Part B

- ELX Dosage

Subjects in the higher weight range were administered ELX 200 mg qd. The appropriate weight cut-off for the switch from 100 mg qd to 200 mg qd was determined based on population-PK modelling that was updated with preliminary PK data from Part A and data from studies conducted in adult and adolescent CF subjects.

- TEZ and IVA Dosages

TEZ was administered as 50 mg qd and IVA was administered as 75 mg every 12 hours (q12h) in all subjects in Part A and in subjects weighing <30 kg in Part B. In Part B, doses of TEZ 100 mg qd and IVA 150 mg q12h were administered in subjects weighing ≥30 kg. The dosages and weight cut-off were selected based on an evaluation of PK and safety of TEZ/IVA in CF subjects 6 to 11 years of age in Part A of Study 661-113.

Table 4 Parts A and B Doses

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
All subjects	100 mg qd	50 mg qd	75 mg q12h
Part B			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h

ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Treatment modification, interruption and discontinuation

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

- Liver Function Tests

In subjects who interrupted study drug for >72 hours for any reason, the investigator resumed the study drug only after a thorough investigation of the cause for the interruption. The medical monitor was to be notified.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, with or without total bilirubin >2 × ULN, were followed closely, including confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT, AST, and bilirubin levels, as clinically indicated. If a subject could not return to the site for confirmatory testing, the use of a local laboratory was permitted.

Study drug administration was interrupted immediately (prior to confirmatory testing) if any of the following criteria were 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.

A thorough investigation of potential causes was conducted, and the subject was followed closely for clinical progression.

Study drug administration was discontinued if the following criteria were met:

- Subsequent ALT or AST values confirmed the initial elevation that satisfied the interruption rule (above), and no convincing alternative aetiology was identified, regardless of whether transaminase levels had improved.

All subjects in whom treatment was discontinued for elevated transaminases (and bilirubin, as applicable) had these levels monitored closely until levels normalized or returned to baseline.

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice was identified, study drug administration was permitted to resume once transaminases returned to baseline or were ≤2 × ULN, whichever was higher. Regardless of the duration of the interruption, the medical monitor was notified prior to resumption of the study drug.

Upon resumption of the study drug, transaminases and bilirubin were assessed weekly for 4 weeks.

If a protocol-defined transaminase elevation interruption threshold recurred 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 was permanently discontinued, regardless of the presumed etiology.

- Rash

Individuals who developed a generalized rash were monitored closely. Study drug dosing was interrupted if a subject developed a generalized rash of Grade 3 or higher, or a rash that was considered a serious adverse event (SAE). The investigator notified the medical monitor of any rash that resulted in interruption of study drug, is Grade 3 or higher or was an SAE. Investigators were to consider additional evaluation including laboratory testing (e.g., complete blood count with differential, liver function tests [LFTs]), photographs of the rash, and dermatology consultation. The investigator could consider resumption of study drug if considered clinically appropriate.

Objectives

Primary Objectives

Part A: To evaluate the pharmacokinetics (PK) of ELX, TEZ, and IVA when dosed in TC

Part B: To evaluate the safety and tolerability of ELX/TEZ/IVA through Week 24

Secondary Objectives

Part A

• To evaluate the PK of ELX, TEZ, and IVA metabolites

• To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

• To evaluate the efficacy of ELX/TEZ/IVA through Week 24

• To evaluate the PK of ELX, TEZ, and IVA

• To evaluate the PK of ELX, TEZ, and IVA metabolites

Outcomes/endpoints

The criteria for evaluation are displayed below:

Part A

- Primary: PK of ELX, TEZ, and IVA when dosed in TC
- Secondary:
  - PK of ELX, TEZ, and IVA metabolites
  - safety and tolerability of ELX/TEZ/IVA

Part B

- Primary: safety and tolerability of ELX/TEZ/IVA through Week 24:

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

- Secondary:
  - PK of ELX, TEZ, and IVA metabolites
  - Efficacy and PD:

    Spirometry and sweat chloride (SwCl)

    Weight, height, body mass index (BMI), Cystic Fibrosis Questionnaire-Revised (CFQ-R), multiple-breath washout, and other events related to outcome (e.g., pulmonary exacerbations [PEx])

    Exploratory: Faecal elastase-1 (FE-1) and immunoreactive trypsinogen (IRT) to assess exocrine pancreatic function

Spirometry

The following measured spirometric values were converted to percent predicted values using the standard equations of GLI: FEV1 (L), forced vital capacity (FVC) (L), FEV1/FVC (ratio), and forced expiratory flow, midexpiratory phase (L/s).

Multiple-breath Washout (N2-MBW)

The final LCI value at each visit was the value provided by the LCI vendor based on the replicates.

During the Screening Period, the MBW test could be performed pre- or post-bronchodilator. At all other visits, all MBW tests were performed "pre-bronchodilator"

Drug Acceptability Assessment

The acceptability of study drug was assessed by the investigator and authorized designee through the Modified Facial Hedonic Scale.

Subjects were observed for their facial expressions, and the reaction was scored using a visual analog scale; any spontaneous comments in regard to likes or dislikes were also noted.

Randomisation and blinding (masking)

Part B

Approximately 56 subjects (F/F or F/MF genotypes) were planned for enrolment to ensure approximately 45 subjects completed Part B. Target enrolment was approximately 25 subjects with F/MF genotypes and 20 subjects with F/F genotypes.

As all subjects were treated identically, no randomization was planned.

This was an open-label study. However, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) were not informed of their study-related spirometry and LCI, sweat chloride (SwCl), faecal elastase-1 (FE-1), and immunoreactive trypsinogen (IRT) results during the Treatment Period, regardless of whether the subject permanently discontinued treatment.

Statistical methods

- PK Analyses

Individual concentration values of each analyte (ELX, TEZ, IVA, and relevant metabolites) were listed, and summary statistics for concentrations of each analyte were presented.

- Efficacy and PD Analyses

Part A

Efficacy was not an objective of Part A. Descriptive statistics based on the Full Analysis Set (FAS) were summarized for spirometry; SwCl; and weight, height, BMI, and their respective z-scores.

Part B

As efficacy is a secondary objective of the study, there was no multiplicity adjustment; all P values are considered nominal.

Table 5 describes the main efficacy analyses based on the FAS. Each continuous efficacy and PD endpoint was analysed using a mixed-effects model for repeated measures that included visit as the fixed effect, with the 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), whether assessed on treatment or after treatment discontinuation.

Table 5 Efficacy and PD Endpoints and Methods

Endpoint	Method of Analysis
Primary Efficacy Endpoint	
Not applicable	Not applicable
Secondary Efficacy and PD Endpoints	
Absolute change in ppFEV$_1$ from baseline through Week 24	• MMRM with clinic-assessed spirometry data only • LS mean (95% CI) and *P* value through Week 24 • Line plot • Sensitivity analysis (multiple imputation analysis) • Ad hoc subgroup analysis by genotype group (F/F or F/MF)
Absolute change in SwCl from baseline through Week 24	• MMRM • LS mean (95% CI) and *P* value through Week 24 • Line plot • Ad hoc subgroup analysis by genotype group (F/F or F/MF)
Absolute change in CFQ-R RD score (Child's Version) from baseline through Week 24	• MMRM with clinic-assessed data only • LS mean (95% CI) and *P* value through Week 24 • Line plot • Ad hoc subgroup analysis by genotype group (F/F or F/MF)
Absolute change in BMI and BMI-for-age z-score from baseline at Week 24	• MMRM • LS mean (95% CI) and *P* value at Week 24 • Line plot
Absolute change in weight and weight-for-age z-score from baseline at Week 24	• MMRM • LS mean (95% CI) and *P* value 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) and *P* value at Week 24 • Line plot
Drug acceptability assessment using Modified Facial Hedonic Scale	• Descriptive statistics (by category) with clinic-assessed data only
Number of PEx and CF-related hospitalizations through Week 24	• Descriptive statistics (annualized event rate)
Absolute change in LCI$_{2.5}$ from baseline through Week 24	• MMRM • LS mean (95% CI) and *P* value through Week 24 • Line plot • Ad hoc subgroup analysis by genotype group (F/F or F/MF)
Other/Exploratory Efficacy Endpoints	
Absolute change in FE-1 levels from baseline at Week 24	• Descriptive statistics • Shift from baseline analysis
Absolute change in serum levels of IRT from baseline at Week 24	• Descriptive statistics • Shift from baseline analysis

BMI: body mass index; CF: cystic fibrosis; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; COVID-19: coronavirus disease; 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; MMRM: mixed-effects model for repeated measures; PD: pharmacodynamic; PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

Note: Due to the COVID-19 pandemic, spirometry (ppFEV$_1$), CFQ-R RD score, and the drug acceptability assessment were permitted to be assessed independently by the subjects (and the subject's parent/caregiver, as applicable) at home; these home-assessed data were not included in the clinic-assessed only analyses.

- Safety Analyses

All safety analyses were conducted for Parts A and B separately, based on data from the corresponding Treatment-emergent (TE) Period in the Safety Set (Table 6). The overall safety profile of the study drug was assessed in terms of the following safety and tolerability endpoints: treatment-emergent adverse events (TEAEs), clinical laboratory values, standard 12-lead ECGs, vital signs, pulse oximetry, and ophthalmologic examinations. All AEs were coded according to MedDRA and were classified as pre-treatment, treatment-emergent, or post-treatment. Only descriptive analysis of safety was performed; no statistical testing was performed. For the results, discussion, and conclusions in this clinical study report, TEAEs are referred to as AEs.

Table 6 Safety Data Summaries

Assessment	Incidence	Raw Value and Change From Baseline	Subject Listing	Threshold Analysis	Shift From Baseline	Plot of Max Values
TEAEs	X		X			
Non-LFT chemistry		X	X	Selected parameters; Part B only		
LFT chemistry		X	X	X	X	Part B only
Hematology and coagulation		X	X	Selected parameters; Part B only		
Urinalysis			X			
Urine or serum pregnancy test			X			
12-lead ECGs		X	X	Selected parameters		
Vital signs		X	X	Selected parameters		
Pulse oximetry		X	X		X	
PEs			X			
OEs			X			

LFT: liver function test; OE: ophthalmologic examination; PE: physical examination; TEAE: treatment-emergent adverse event
Note: Analyses apply to both Parts A and B unless otherwise specified.

Analyses Sets

Safety Set

The Safety Set will include all subjects who received at least 1 dose of the study drug. The Safety Set will be used for all safety analyses.

Full Analysis Set (FAS)

The FAS will include all subjects who are enrolled and carry the intended *CFTR* allele mutation and received at least 1 dose of the study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy and PD endpoints, unless otherwise specified.

All Subjects Set

The All Subjects Set will include all subjects who are enrolled or received at least 1 dose of the study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

Results

Participant flow

Study Participant flow

In Part A, 16 subjects received at least 1 dose of study drug, all of whom completed study drug treatment and the study.

In Part B, 66 subjects received at least 1 dose of study drug, 64 (97.0%) of whom completed study drug treatment and the study; 1 subject discontinued due to an AE, and 1 subject withdrew consent (not due to AE).

Table 7 Subject Disposition (All Subjects Set, Part B)

Disposition	ELX/TEZ/IVA n (%)
All Subjects Set	66
FAS	66
Safety Set	66
Completed treatment	64 (97.0)
Prematurely discontinued treatment	2 (3.0)
Reason for discontinuation of treatment	
AE	1 (1.5)
Other[a]	1 (1.5)
Completed study	64 (97.0)
Prematurely discontinued the study	2 (3.0)
Reason for discontinuation from study	
AE	1 (1.5)
Withdrawal of consent (not due to AE)	1 (1.5)
Rollover to the extension study	64 (97.0)

Source: Table 14.1.1b
AE: adverse event; COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor
Note: The All Subjects Set included all subjects who were enrolled or received at least 1 dose of study drug (in Part B). The FAS included all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. The Safety Set included all subjects who received at least 1 dose of study drug.
[a] The subject did not want to leave home due to the COVID-19 pandemic and therefore switched to commercially available drug (Listing 16.2.1b).

Recruitment

Part B

In Part B, subjects were enrolled at 21 sites in North America, Europe, and Australia.

Study initiation: 05 August 2019 (date first eligible subject signed the informed consent form)

Study completion: 07 August 2020 (date last subject completed the last visit)

Conduct of the study

Data lock

The date of data lock for Study VX18-445-106 (Study 106) Part A was 21 February 2019 and for Part B was 24 August 2020.

Changes in study protocol

The study protocol was amended twice.

- Changes in the SAP

There were no changes to the SAP. The current SAP Version 3.0 is dated 11 August 2020.

- Changes in Study Conduct Due to COVID-19

Vertex implemented safety measures to provide subjects with the opportunity to continue participation in Study 106 Part B while ensuring their safety by minimizing the risk to COVID-19 exposure through travel; the conduct of Part A was not impacted by the COVID-19 pandemic. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to study integrity.

Implemented measures were enabled based on the country and local regulations and site-level considerations (e.g., whether sites had subjects actively participating in Study 106, or site closures due to COVID-19).

In particular, subjects who missed the Week 24 visit were requested to return and complete an unscheduled visit to capture safety laboratory testing missed due to the COVID-19 pandemic, as well as any AEs related to laboratory testing. If feasible, efficacy data (spirometry, SwCl, and LCI) were also collected at the same unscheduled visit, but this was not mandatory.

In addition to their usual review of central laboratory data, investigators were responsible for reviewing local laboratory data to identify potential AEs. These data were entered into this database if all supporting documentation (e.g., laboratory certification) were received; available local laboratory data were provided in individual subject listings.

Table 8- Summary of Implemented Measures to Minimize Risk to COVID-19 Exposure

Addendum Number	Date Finalized	Key Changes and Rationale	Date Implemented
1.0	24 April 2020	Remote consent was permitted to minimize COVID-19 exposure. ICF forms were then signed and dated before sending to the site via post mail.	17 March 2020
		Study drug was permitted to be dispensed to subjects outside of the context of an in-clinic visit (e.g., shipped directly from the site to the subject), as applicable, and if permitted by local regulations.	17 March 2020
		Study visits were permitted to be conducted as in-home visits by qualified personnel. In addition, all subjects were permitted to be contacted by site personnel by telephone/video call.	In-home visits: 05 May 2020 Telephone/video contact: 16 March 2020
		Safety assessments were permitted to be performed by qualified personnel conducting the in-home visits. Blood and/or urine samples for safety assessments were permitted to be collected and analyzed at local laboratories for subjects who did not have in-home visits, but did not complete the assessment at the site. In addition, safety assessents were permitted to be evaluated by telephone.	In-home safety assessments: 05 May 2020 Telephone safety assessments: 16 March 2020 Use of local laboratories: 17 March 2020
		Efficacy assessments (i.e., spirometry, CFQ-R, Modified Facial Hedonic Scale) were permitted to be performed by subjects at home.[a]	In-home spirometry: 06 May 2020 In-home CFQ-R: 06 May 2020 In-home Modified Facial Hedonic Scale: 06 May 2020
		Remote monitoring visits, including remote source data verification, were permitted as allowed per local regulations. The study team reviewed the risk assessment and prioritized data based on primary endpoints, key secondary endpoints, and safety as detailed in the monitoring plan.	24 April 2020
2.0[b]	15 May 2020	Provided examples of qualified personnel (e.g., personnel from site or qualified health care agency) who could conduct safety assessments, as indicated per protocol, during in-home visits.	15 May 2020

3.0	29 July 2020	Enabled unscheduled visits to be performed during the study (including after the protocol defined last study visit) at the discretion of the investigator or Vertex, in the event that assessments specified to be collected at a scheduled visit were not collected due to COVID-19; this change was implemented after all subjects in the study had completed their last scheduled visit.	21 July 2020

CFQ-R: Cystic Fibrosis Questionnaire – Revised; COVID-19: coronavirus disease; SwCl: sweat chloride

[a] Addendum 1 also allowed for SwCl to be collected at home. However, this measure was not enabled for Study 106; all SwCl assessments occurred in clinic.

[b] Addendum 2 also allowed for weight and height to be collected by subjects or their caregivers using medical grade scales and stadiometers; however, data from these devices was not included in Study 106.

Baseline data

Demographics and Other Baseline Characteristics

The mean population age was 9.3 years, and over half (59.1%) of the subjects were female. The majority of subjects (87.9%) were White, and none were Hispanic or Latino. A total of 29 (43.9%) subjects had an F/F genotype, and 37 (56.1%) subjects had F/MF genotypes, with 15 distinct F/MF genotypes represented. At baseline, the mean ppFEV$_1$ was 88.8 and mean SwCl was 102.2 mmol/L. The most common concomitant medications were typically used for the management of CF.

Table 9 Subject Demographics (FAS, Part B)

Demographic	ELX/TEZ/IVA N = 66
Sex, n (%)	
Male	27 (40.9)
Female	39 (59.1)
Childbearing potential[a], n (%)	
Yes	39 (100.0)
No	0
Age at baseline (years)	
n	66
Mean (SD)	9.3 (1.9)
Median	9.6
Min, max	6.1, 12.1[b]
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	58 (87.9)
Not collected per local regulations	8 (12.1)
Race, n (%)	
White	58 (87.9)
Asian	1 (1.5)
Not collected per local regulations	8 (12.1)
Geographic region, n (%)	
North America	47 (71.2)
Europe and Australia	19 (28.8)

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.
[a] Percentages of childbearing females were based on the number of females in the FAS. In Part A, which was conducted under Version 1.0 of the protocol, childbearing potential was defined as female subjects ≥10 years of age. In Part B, conducted under Version 2.0 or later, no age limit was placed on childbearing potential.
[b] One subject provided written informed consent/assent several days before her 12th birthday but enrolled after reaching 12 years of age.

Prior and Concomitant Medications

Table 10 summarizes concomitant medications received by at least 20% of subjects overall by PN. The most common concomitant medications were typically used for the management of CF.

Table 10 Concomitant Medications Received by At Least 20% of Subjects by PN (FAS, Part B)

Preferred Name	ELX/TEZ/IVA N = 66 n (%)
Subjects with any concomitant medication	66 (100.0)
Sodium chloride	57 (86.4)
Dornase alfa	55 (83.3)
Salbutamol	53 (80.3)
Pancreatin	46 (69.7)
Fluticasone propionate	23 (34.8)
Ascorbic acid/ betacarotene/ biotin/ calcium pantothenate/ colecalciferol/ cyanocobalamin/ folic acid/ nicotinamide/ phytomenadione/ pyridoxine hydrochloride/ retinol palmitate/ riboflavin/ thiamine mononitrate/ tocopherol/ zinc ascorbate	20 (30.3)
Azithromycin	20 (30.3)
Ibuprofen	20 (30.3)
Pancrelipase	19 (28.8)
Macrogol 3350	18 (27.3)
Paracetamol	17 (25.8)
Omeprazole	16 (24.2)
Salbutamol sulfate	14 (21.2)
Vitamins NOS	14 (21.2)

Source: Table 14.1.6.2b
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NOS: not otherwise specified; PN: Preferred Name; TE: treatment-emergent; TEZ: tezacaftor; WHODrug: World Health Organization Drug Dictionary
Notes: Medications were coded using WHODrug Global, version March 2020, format B3. PNs were sorted in descending order of frequency. A subject with multiple medications with the same PN was counted only once for that PN. Concomitant medication was defined as medication that was continued or newly received during the TE Period of Part B.

Numbers analysed

A total of 66 subjects were enrolled and received at least 1 dose of the study drug, and 64 (97.0%) subjects completed treatment and the study. One subject discontinued due to an AE, and 1 subject withdrew consent (not due to AE) (Table 7).

Outcomes and estimation

- **Absolute Change in ppFEV1**

Part A

Summary statistics for post-baseline raw values and changes from baseline are provided for ppFEV1 and other lung function parameters; both absolute and relative changes are summarized. On Day 15, the within-group mean (SD) absolute change from baseline in ppFEV1 was 11.8 (8.9) percentage points.

Part B

The main analysis of absolute change in ppFEV1 from baseline through Week 24 (clinic assessed) is presented in Table 11 and Figure 5.

Treatment with ELX/TEZ/IVA resulted in within-group improvements through Week 24. The LS mean absolute change in ppFEV1 from baseline through Week 24 was 10.2 percentage points (95% CI: 7.9, 12.6; P<0.0001).

Table 11 MMRM Analysis of Absolute Change From Baseline in ppFEV1 Through Week 24 (FAS, Part B)

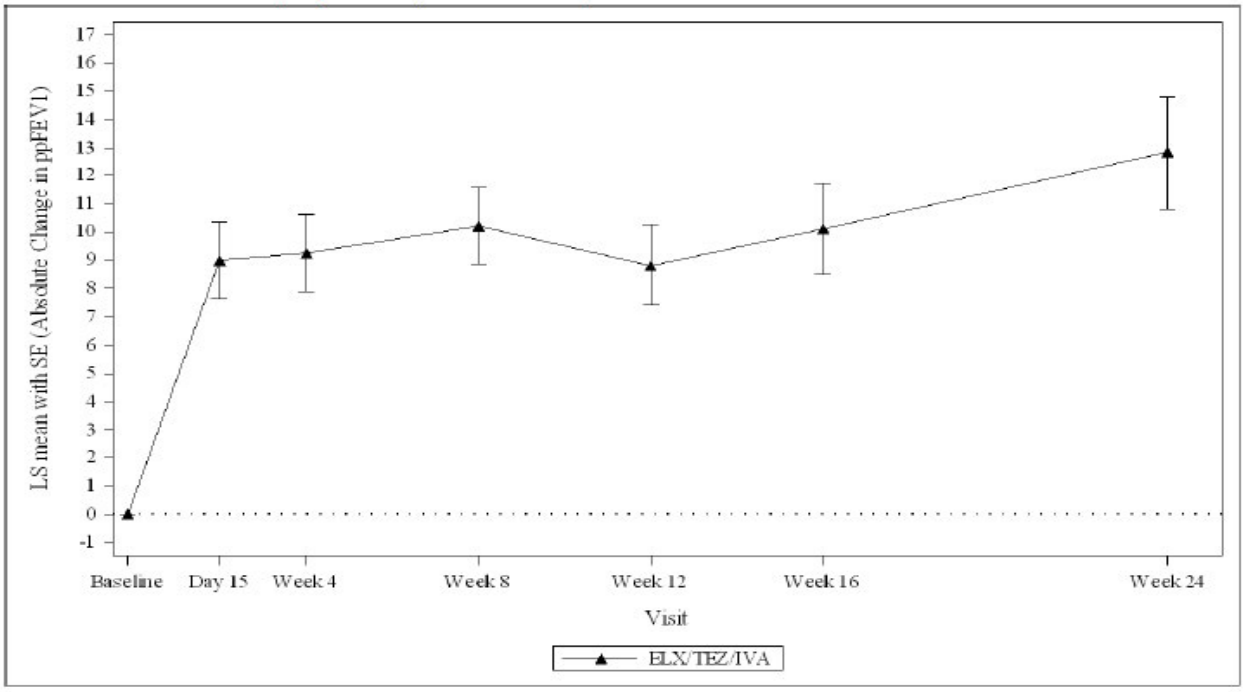
	ELX/TEZ/IVA N = 66
Baseline	
n	62
Mean (SD)	88.8 (17.7)
Absolute change through Week 24	
n	59
LS mean (SE)	10.2 (1.2)
95% CI of LS mean	(7.9, 12.6)
P value	<0.0001

Source: Table 14.2.1.2b

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; 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 clinic-assessed data up to Week 24, with visit as fixed effect and baseline $ppFEV_1$ and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetry covariance structure was used to model the within-subject errors.

Figure 4 MMRM Analysis of Absolute Change From Baseline in ppFEV1 (Percentage Points) 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; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; 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 clinic-assessed data up to Week 24, with visit as fixed effect and baseline $ppFEV_1$ and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetry covariance structure was used to model the within-subject errors.

Table 12 presents subjects with ppFEV1 data by visit for the main analysis (clinic-based assessments) and the additional analysis including clinic-assessed data collected from unscheduled visits conducted after Week 24 (due to the COVID-19 pandemic).

Table 12 Number of Subjects With Data by Visit in the Main MMRM Analysis and an Additional MMRM Analysis for ppFEV1 (FAS, Part B)

	Number of Subjects With Data at Time Point, n							
		Absolute Change at						
	Baseline	D15	WK4	WK8	WK12	WK16	WK24	WK24-U[a]
ELX/TEZ/IVA (N=66)	62	51	52	51	43	29	15	24

Source: Table 14.2.1.3b and Table 14.2.1.9b

COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; U: unscheduled

[a] WK24-U includes subjects who had $ppFEV_1$ data collected at unscheduled visits conducted after Week 24 (the primary purpose of these visits was to capture safety laboratory testing missed due to the COVID-19 pandemic).

Sensitivity and Additional Analyses

A sensitivity analysis was performed using the multiple imputation method to assess for impact of missing data; MMRM results for the through Week 24 endpoint were consistent with the main analysis (Absolute change through Week 24 LS mean (SE) is 9.9 (1.0))

An additional prespecified analysis was performed that included home-assessed spirometry (i.e., spirometry assessed independently by the subjects at home) that was permitted due to the COVID-19 pandemic. The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is 10.7 (1.2).

Another prespecified analysis included all clinic-assessed spirometry data collected through completion of study participants using the extended analysis visit windows (i.e., including data from unscheduled visits that were conducted after Week 24 to capture safety laboratory testing missed due to the COVID-19 pandemic). The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is 10.2 (1.3)).

- **Absolute Change in SwCl From Baseline Through Week 24**

Part A

On Day 15, the within-group mean (SD) change from baseline in SwCl was -50.9 (13.1) mmol/L.

Part B

Treatment with ELX/TEZ/IVA resulted in within-group improvements (reductions) through Week 24. The LS mean absolute change in SwCl from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2; P<0.0001) (Table 13, Figure 6).

Table 13 MMRM Analysis of Absolute Change From Baseline in SwCl Through Week 24 (FAS, Part B)

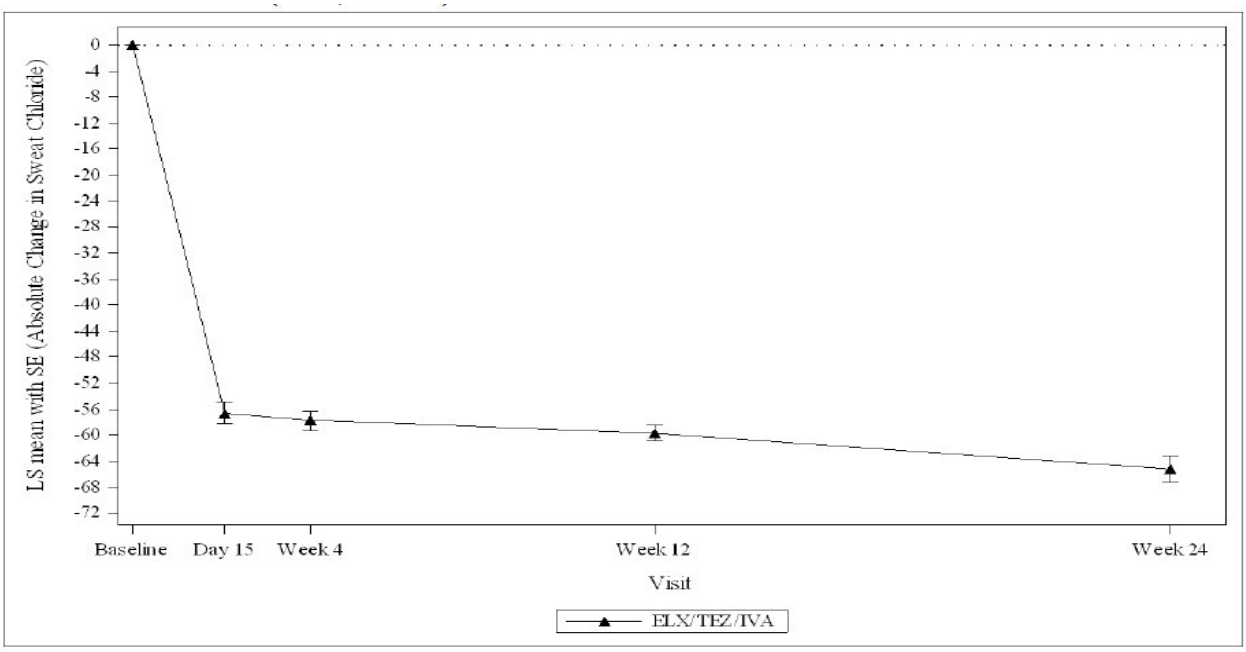
	ELX/TEZ/IVA N = 66
Baseline	
n	62
Mean (SD)	102.2 (9.1)
Absolute change through Week 24	
n	60
LS mean (SE)	-60.9 (1.4)
95% CI of LS mean	(-63.7, -58.2)
P value	<0.0001

Source: Table 14.2.2.2b

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 up to Week 24, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Figure 5 MMRM Analysis of Absolute Change From Baseline in SwCl (mmol/L) by Visit (FAS, Part B)



Source: Figure 14.2.2b
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; 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 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.

Table 14 presents subjects with SwCl data by visit for the main analysis and the additional analysis including data collected from unscheduled visits conducted after Week 24 (due to the COVID-19 pandemic).

Table 14 Number of Subjects With Data by Visit in the Main and Additional MMRM Analyses for SwCl (FAS, Part B)

	Number of Subjects With Data at Time Point, n					
		Absolute Change at				
	Baseline	D15	WK4	WK12	WK24	WK24-U[a]
ELX/TEZ/IVA (N=66)	62	56	56	50	28	40

Source: Table 14.2.2.3b and Table 14.2.2.5b
COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SwCl: sweat chloride; TEZ: tezacaftor; U: unscheduled
[a] WK24-U includes subjects who had SwCl data collected at unscheduled visits conducted after Week 24 (the primary purpose of these visits was to capture safety laboratory testing missed due to the COVID-19 pandemic).

Additional Analysis

A prespecified analysis was performed that included all SwCl data collected through completion of study participation, including at unscheduled visits after Week 24. The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is -61.4 (1.3).

- **Absolute Change in CFQ-R Respiratory Domain Score (Child's Version) From Baseline Through Week 24**

Treatment with ELX/TEZ/IVA resulted in within-group improvements through Week 24. The LS mean absolute change in CFQ-R RD score from baseline through Week 24 was 7.0 points (95% CI: 4.7, 9.2; P<0.0001).

Additional Analysis

An additional prespecified analysis was performed based on pooled CFQ-R RD scores assessed at the clinic and at home. The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is 7.0 (1.1).

- **Absolute Change in BMI, Weight, Height, and Associated Z-Scores From Baseline at Week 24**

Analyses of absolute change in growth parameters (BMI, weight, height, and associated z-scores) from baseline at Week 24 are presented in Table 15.

Table 15 MMRM Analysis of Absolute Change From Baseline in BMI, Weight, Height, and Associated Z-Scores At Week 24 (FAS, Part B)

	ELX/TEZ/IVA N = 66
BMI (kg/m^2)	
Baseline	
n	66
Mean (SD)	16.39 (1.69)
Absolute change at Week 24	
n	33
LS mean (SE)	1.02 (0.13)
95% CI of LS mean	(0.76, 1.28)
P value	<0.0001

BMI z-score	
Baseline	
n	66
Mean (SD)	-0.16 (0.74)
Absolute change at Week 24	
n	33
LS mean (SE)	0.37 (0.05)
95% CI of LS mean	(0.26, 0.48)
P value	<0.0001
Weight (kg)	
Baseline	
n	66
Mean (SD)	30.0 (7.7)
Absolute change at Week 24	
n	33
LS mean (SE)	3.0 (0.2)
95% CI of LS mean	(2.5, 3.5)
P value	<0.0001
Weight z-score	
Baseline	
n	66
Mean (SD)	-0.22 (0.76)
Absolute change at Week 24	
n	33
LS mean (SE)	0.25 (0.04)
95% CI of LS mean	(0.16, 0.33)
P value	<0.0001
Height (cm)	
Baseline	
n	66
Mean (SD)	134.1 (12.3)
Absolute change at Week 24	
n	33
LS mean (SE)	2.3 (0.2)
95% CI of LS mean	(1.9, 2.7)
P value	<0.0001
Height z-score	
Baseline	
n	66
Mean (SD)	-0.11 (0.98)
Absolute change at Week 24	
n	33
LS mean (SE)	-0.05 (0.03)
95% CI of LS mean	(-0.12, 0.01)
P value	0.1057

Sources: Table 14.2.4.1.2b, Table 14.2.4.1.4b, Table 14.2.4.2.2b, Table 14.2.4.2.4b, Table 14.2.4.3.2b, and Table 14.2.4.3.4b

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; LS: least squares; 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 value of the relevant growth parameter (BMI, weight, height, or associated z-score) 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.

- **Number of PEx and CF-related Hospitalizations Through Week 24**

The annual event rate for PEx overall was 0.12 events/year. Event rates for PEx requiring hospitalization and/or IV antibiotic therapy were each 0.03 events/year (Table 16).

The annual event rates for planned and unplanned CF-related hospitalizations were each 0 events/year.

Table 16 Summary of PEx During the PEx Analysis Period (FAS, Part B)

	ELX/TEZ/IVA N = 66
Total number of days (years) of the PEx analysis period	11060 (32.9)
PEx overall	
Number of subjects with events, n (%)	4 (6.1)
Number of events	4
Observed event rate per year	0.12
PEx requiring hospitalization	
Number of subjects with events, n (%)	1 (1.5)
Number of events	1
Observed event rate per year	0.03
PEx requiring IV antibiotic therapy	
Number of subjects with events, n (%)	1 (1.5)
Number of events	1
Observed event rate per year	0.03
PEx requiring hospitalization or IV antibiotic therapy	
Number of subjects with events, n (%)	1 (1.5)
Number of events	1
Observed event rate per year	0.03

Source: Table 14.2.6.1b

ELX: elexacaftor; FAS: Full Analysis Set; IV: intravenous; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; TEZ: tezacaftor

Notes: PEx was defined as any new or change in antibiotic therapy (IV, inhaled, or oral) for ≥4 sinopulmonary signs/symptoms (Section 9.5.7.6.1). Total number of days = sum of the individual duration (actual number of days) of the PEx analysis period across all subjects. Total number of years = total number of days / 336. Observed event rate per year = total number of events * 336 / total number of days of the PEx analysis period. The event rate was calculated based on 336 days (48 weeks) in a year.

- **Absolute Change in LCI2.5 From Baseline Through Week 24**

Treatment with ELX/TEZ/IVA resulted in within-group improvements (reductions) through Week 24. The LS mean absolute change in LCI2.5 from baseline through Week 24 was -1.71 (95% CI: -2.11, -1.30; P<0.0001).

Table 17 MMRM Analysis of Absolute Change From Baseline in LCI2.5 Through Week 24 (FAS, Part B)

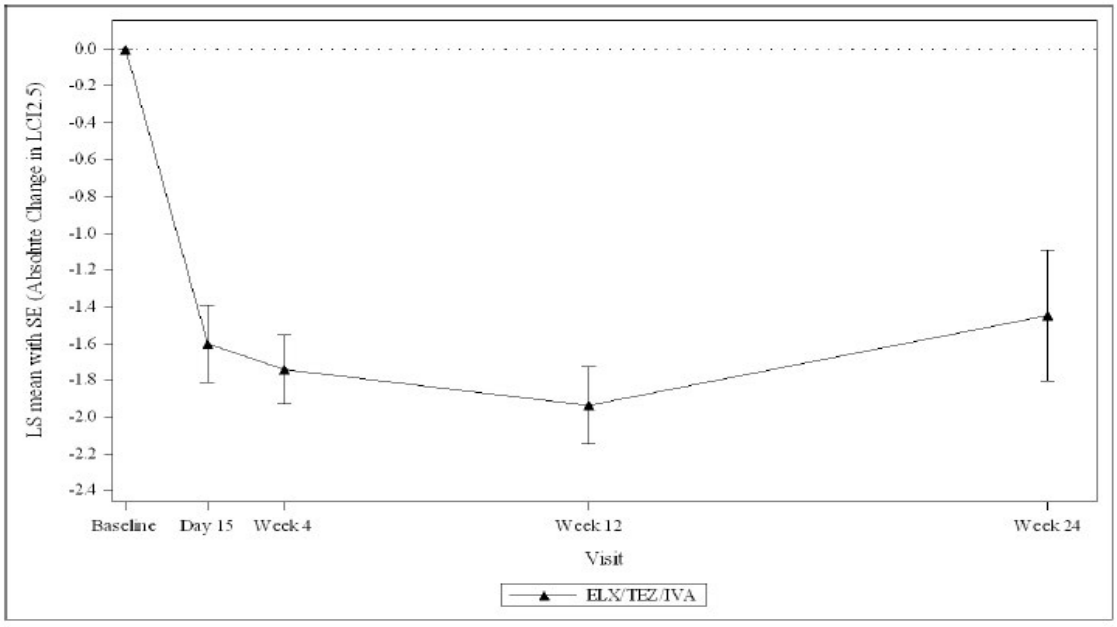
	ELX/TEZ/IVA N = 66
Baseline	
n	53
Mean (SD)	9.77 (2.68)
Absolute change through Week 24	
n	50
LS mean (SE)	-1.71 (0.20)
95% CI of LS mean	(-2.11, -1.30)
P value	<0.0001

Source: Table 14.2.7.2b

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; 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 up to Week 24, with visit as fixed effect and baseline $LCI_{2.5}$ and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Figure 6 MMRM Analysis of Absolute Change From Baseline in LCI2.5 by Visit (FAS, Part B)



Source: Figure 14.2.5b

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; MMRM: mixed-effects model for repeated measures; 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 $LCI_{2.5}$ 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.

Additional Analysis

A prespecified additional analysis was performed that included all LCI2.5 data collected through completion of study participation, including at unscheduled visits after Week 24. The MMRM results for the through Week 24 endpoint were consistent with the main analysis.

- **Drug Acceptability Assessment Using Modified Facial Hedonic Scale**

Clinic-assessed results of the drug acceptability assessment (subject reaction) using the modified facial hedonic scale at Week 24 showed that the majority of subjects either "liked it very much" or "liked it a little" at Week 24; results were similar at other evaluation time points.

Ancillary analyses

Upon request from the CHMP, the MAH provided additional analyses of the within-group change through week 12, with all week 16 and week 24 data excluded from the analysis.

Table 18 Modified MMRM Analysis of Absolute Change From Baseline in ppFEV1 Through Week 12 (FAS, Study 106 Part B)

	ELX/TEZ/IVA N = 66
Baseline	
n	62
Mean (SD)	88.8 (17.7)
Absolute change through Week 12	
n	59
LS mean (SE)	9.6 (1.1)
95% CI of LS mean	(7.3, 11.9)
P value	<0.0001

Source: Ad hoc Table 14.2.1.14b

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; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline $ppFEV_1$, visit*(baseline $ppFEV_1$) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4, 8, and 12 (clinic-assessed data only) were included in the estimation of the average treatment effect through Week 12.

Table 19 Modified MMRM Analysis of Absolute Change From Baseline in SwCl Through Week 12 (FAS, Study 106 Part B)

	ELX/TEZ/IVA N = 66
Baseline	
n	62
Mean (SD)	102.2 (9.1)
Absolute change through Week 12	
n	59
LS mean (SE)	-58.6 (1.3)
95% CI of LS mean	(-61.1, -56.1)
P value	<0.0001

Source: Ad hoc Table 14.2.2.14b

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; *P*: probability; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline SwCl, visit*(baseline SwCl) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4 and 12 were included in the estimation of the average treatment effect through Week 12.

Table 20 Modified MMRM Analysis of Absolute Change From Baseline in CFQ-RRD Score (Child's Version) Through Week 12 (FAS, Study 106 Part B)

	ELX/TEZ/IVA N = 66
Baseline	
n	65
Mean (SD)	80.3 (15.2)
Absolute change through Week 12	
n	65
LS mean (SE)	5.6 (1.3)
95% CI of LS mean	(2.9, 8.2)
P value	<0.0001

Source: Ad hoc Table 14.2.3.14b

CFQ-R: Cystic Fibrosis Questionnaire-Revised; 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; *P*: probability; RD: respiratory domain; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline CFQ-R RD score, visit*(baseline CFQ-R RD score) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4, 8, and 12 (clinic-assessed data only) were included in the estimation of the average treatment effect through Week 12.

Table 21 Modified MMRM Analysis of Absolute Change From Baseline in LCI2.5 Through Week 12 (FAS, Study 106 Part B)

	ELX/TEZ/IVA N = 66
Baseline	
n	53
Mean (SD)	9.77 (2.68)
Absolute change through Week 12	
n	48
LS mean (SE)	-1.83 (0.17)
95% CI of LS mean	(-2.18, -1.49)
P value	<0.0001

Source: Ad hoc Table 14.2.7.9b

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; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline $LCI_{2.5}$, visit*(baseline $LCI_{2.5}$) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4 and 12 were included in the estimation of the average treatment effect through Week 12.

Table 22 MMRM Analysis of Absolute Change From Baseline in BMI, Weight, Height, and Associated Z-scores At Weeks 12 and 24 (FAS, Study 106 Part B)

	ELX/TEZ/IVA N = 66
BMI (kg/m^2)	
Baseline	
n	66
Mean (SD)	16.39 (1.69)
Absolute change at Week 12	
n	58
LS mean (SE)	0.49 (0.09)
95% CI of LS mean	(0.32, 0.67)
Absolute change at Week 24	
n	33
LS mean (SE)	1.02 (0.13)
95% CI of LS mean	(0.76, 1.28)
P value	<0.0001
BMI z-score	
Baseline	
n	66
Mean (SD)	-0.16 (0.74)
Absolute change at Week 12	
n	58
LS mean (SE)	0.22 (0.04)
95% CI of LS mean	(0.13, 0.30)
Absolute change at Week 24	
n	33
LS mean (SE)	0.37 (0.05)
95% CI of LS mean	(0.26, 0.48)
P value	<0.0001

Weight (kg)	
Baseline	
n	66
Mean (SD)	30.0 (7.7)
Absolute change at Week 12	
n	58
LS mean (SE)	1.4 (0.2)
95% CI of LS mean	(1.1, 1.7)
Absolute change at Week 24	
n	33
LS mean (SE)	3.0 (0.2)
95% CI of LS mean	(2.5, 3.5)
P value	<0.0001
Weight z-score	
Baseline	
n	66
Mean (SD)	-0.22 (0.76)
Absolute change at Week 12	
n	58
LS mean (SE)	0.13 (0.03)
95% CI of LS mean	(0.07, 0.18)
Absolute change at Week 24	
n	33
LS mean (SE)	0.25 (0.04)
95% CI of LS mean	(0.16, 0.33)
P value	<0.0001

Height (cm)	
Baseline	
n	66
Mean (SD)	134.1 (12.3)
Absolute change at Week 12	
n	58
LS mean (SE)	1.1 (0.1)
95% CI of LS mean	(1.0, 1.3)
Absolute change at Week 24	
n	33
LS mean (SE)	2.3 (0.2)
95% CI of LS mean	(1.9, 2.7)
P value	<0.0001
Height z-score	
Baseline	
n	66
Mean (SD)	-0.11 (0.98)
Absolute change at Week 12	
n	58
LS mean (SE)	-0.03 (0.02)
95% CI of LS mean	(-0.06, 0.00)
Absolute change at Week 24	
n	33
LS mean (SE)	-0.05 (0.03)
95% CI of LS mean	(-0.12, 0.01)
P value	0.1057

Sources: Study 106 CSR/Tables 14.2.4.1.2b, 14.2.4.1.4b, 14.2.4.2.2b, 14.2.4.2.4b, 14.2.4.3.2b, and 14.2.4.3.4b

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; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; TEZ: tezacaftor

Notes: 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 value of the relevant growth parameter (BMI, weight, height, or associated z-score) 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.

Summary of main efficacy results

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

Table 23 Summary of efficacy for trial VX18-445-106 part B

Title: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age	
Study identifier	VX18-445-106

Design	2-part (Parts A and B), multicenter study Part B: single arm, open-label study in CF subjects 6 through 11 years of age who are heterozygous for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 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 < 30 kg: 100 mg ELX qd/50 mg TEZ qd/75 mg IVA q12h ≥30 kg: 200 mg ELX qd/100 mg TEZ qd/150 mg IVA q12h Duration 24 weeks Number 66 in total
Endpoints and definitions	Secondary endpoint	percent predicted forced expiratory volume in 1 second (ppFEV1) (%)	Absolute change in ppFEV1 from baseline through week 24
	Secondary endpoint	Sweat chloride (SwCl) (mmol/l)	Absolute change in SwCl from baseline through week 24
	Secondary endpoint	Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) (points)	Absolute change in CFQ-R from baseline through week 24
	Secondary endpoint	LCI2.5	Absolute change in LCI2.5 from baseline through week 24
Database lock	24 August 2020		

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	66
	LS mean $ppFEV_1$	10.2
	95% CI of LS mean	7.9, 12.6
	p-value	<0.0001

	LS mean SwCl	-60.9
	95% CI of LS mean	-63.7, -58.2
	p-value	<0.0001
	LS mean CFQ-R RD	7.0
	95% CI of LS mean	4.7,9.2
	p-value	<0.0001
	LS mean LCI2.5	-1.71
	95% CI of LS mean	(-2.11,-1.30)
	p-value	<0.0001
Notes:	Not all of the 66 participants included in the FAS had data available at all timepoints, while most data are missing after week 12 because of COVID pandemic restrictions.	

2.6.3. Discussion on clinical efficacy

The results of Study VX18-445-106 (Study 106) have been submitted to support an indication expansion of ELX/TEZ/IVA to include CF patients 6 through 11 years of age.

Study 106 is a phase 3, multicenter study conducted in 2 parts to evaluate the pharmacokinetics (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are heterozygous for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype).

Design and conduct of clinical studies

In Part A of study 106, patients were treated with ELX/TEZ/IVA 100 mg/50 mg/75 mg FDC tablet and IVA 75 mg tablet for 15 days

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

- subjects <30 kg: ELX100 mg qd/TEZ 50 mg qd/ IVA 75 mg q12h
- subjects ≥ 30 kg: ELX200 mg qd/TEZ 100 mg qd/ IVA 150 mg q12h

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 as well as prohibited medication rules are applied as for the adults in the marketing application studies and are acceptable.

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

Endpoints

As safety is the primary objective in Study 106 Part B, the proposed secondary efficacy endpoints are acceptable. Sweat chloride as a pharmacodynamic parameter is an important parameter for measuring the effect of a modulator. In CF, sweat chloride is increased and a decrease can be considered as an effect on the underlying pathology. Pulmonary function tests, spirometry and multiple breath wash-out

(MBW) for calculating LCI2.5, are considered important to measure an effect on the lungs, one of the most important affected organs in CF. The LCI2.5 can measure changes in the small airways, while the ppFEV1 is more associated with large airways. In CF, the small airways are earlier affected 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.

CFQ-R measures the quality of life, and changes in BMI z-score and height z-score inform over the nutritional status. Thus, all parameters inform about a different aspect of CF and are considered valuable.

Statistics

As study 106 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 and safety and efficacy as in adolescents and adults, a within-group change from baseline is considered acceptable to provide evidence of comparable efficacy with adolescents and adults.

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), whether assessed on treatment or after treatment discontinuation.

For part B, safety measures were implemented to provide subjects with the opportunity to continue participation while ensuring their safety against COVID-19 exposure in alignment with Health Authority guidance. However, the adjustments made to comply with Health Authority guidance due to COVID-19 potentially impact the results of the study results. Overall, the impact on safety results is expected to be minor provided that all the safety parameters were collected, but at a different time. For the efficacy data (i.e. spirometry, SwCl, and LCI) the impact is greater, because it was not mandatory to collect these data at the same unscheduled visit. Giving patients the option to provide efficacy data through an unscheduled visit during the COVID-19 pandemic may have introduced additional biases because the ability and willingness to provide efficacy data during an unscheduled visit is likely to be associated with the health of the patient at the time.

Efficacy data and additional analyses

A total of 66 subjects were enrolled and received at least 1 dose of the study drug, and 64 (97.0%) subjects completed treatment and the study. One subject discontinued due to an AE, and 1 subject withdrew consent (not due to AE).

The mean population age was 9.3 years, and over half (59.1%) of the subjects were female. The majority of subjects (87.9%) were White, and none were Hispanic or Latino. A total of 29 (43.9%) subjects had an F/F genotype, and 37 (56.1%) subjects had F/MF genotypes, with 15 distinct F/MF genotypes represented. About 50% of the patients has already an impaired lung function, as can be expected with these F/MF and F/F mutations, that affect the organs already in early life.

Of the study population, 78.8% of the patients did not use a modulator before. For the patients with F/MF mutations, no modulator therapy is currently authorised under 12 years of age. However, for patients with F/F mutation, TEZ/IVA and LUM/IVA are available as modulator therapy, although TEZ/IVA became only quite recently available. As a consequence, the group of patients with F/F mutation consist of modulator experienced F/F subjects and modulator naïve F/F subjects.

Outcomes and estimation

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

For the main secondary parameter ppFEV1, the LS mean absolute change in ppFEV1 from baseline through Week 24 was 10.2% (95% CI: 7.9, 12.6; P<0.0001). This is generally similar to the results for the adolescent and adult patients in the original marketing authorisation studies. In these studies, LS mean difference from baseline was 14.3 (95% CI 12.7, 15.8) in patients with F/MF mutations and 7.8%, (95% CI 4.8,10.8) for CFTR modulator experienced F/F patients and 13.2%, (95% CI (8.5,17.9) for CFTR modulator naïve F/F patients. The benefit was thus different between the specific subgroups in the adult population, but still clinically relevant. Generally, lung function is better preserved in children compared to adults. Therefore, a slightly lower benefit would be acceptable. However, as normally a decrease in ppFEV1 will occur, an increase of 10.2% is undoubtfully clinically relevant.

Treatment with ELX/TEZ/IVA resulted in the LS mean absolute change in SwCl from baseline through Week 24 of -60.9 mmol/L (95% CI: -63.7, -58.2; P<0.0001). This result is in line with results for the adolescent and adult patients in the original marketing authorisation studies: LS mean difference from baseline -42.2 mmol/L (95% CI: -44.0, -40.4) in patients with F/MF mutations and LS mean difference from baseline was -43.4 mmol/L (95% CI: -46.9, -40.0) for patients with F/F mutations. A reduction of 10 mmol/L in SwCl has been accepted by the CHMP as clinically relevant. The within LS mean absolute change in CFQ-R Respiratory Domain Score of 7.0 points (95% CI: 4.7, 9.2; P<0.0001) was clinically relevant, but less impressive compared with results for the adolescent and adult patients in the original marketing authorisation studies (patients with F/MF mutations 20.2 points (95% CI 17.5,23.0) and patients with F/F mutations 17.4 points 95% CI 11.8,23.0)). However, in children, the quality of life was somewhat less impaired at the start (80 points) compared with the adults and adolescents (68.3 points and 70.6 in study 102 and study 103 respectively). Moreover, the child version is not completely identical to the adult version. Furthermore, COVID-19 could also have influenced the outcome of the CFQ-R. Nevertheless, an increase of 7.0 points is above MCID of 4 points. Therefore, the results are considered clinically relevant.

An improvement in ventilation inhomogeneity measured by $LCI_{2.5}$ is shown by a numerical decrease from baseline. The LS mean absolute change in $LCI_{2.5}$ from baseline through Week 24 was -1.71 (95% CI: -2.11, -1.30; P<0.0001). The use of absolute change from baseline is preferred, because this endpoint will not mask deteriorations over time, if happened. The additional analysis performed at the request of the CHMP of the LS mean absolute change in $LCI_{2.5}$ at week 12 showed that the change was -1.93 (95% CI -2.31, -1.56).

A minimal clinically important difference (MCID) for the $LCI_{2.5}$ is currently not established. Therefore, an effect larger than the natural variability might be regarded as clinically relevant. As the natural variability for the $LCI_{2.5}$ is 1 unit[4] or 15 % of baseline[5], the results are considered relevant by CHMP.

Subgroup analyses for different patient groups showed that ppFEV1 and SwCl were somewhat better in the F/F patients, while the results of $LCI_{2.5}$ were better in the F/MF patients. The results of both populations are generally in line with the overall group. The improvements were in both groups clinically meaningful.

Not all of the 66 participants included in the FAS had data available at all time points because baseline results did not meet the criteria of acceptability. A requested multiple imputation-based method to

[4] Singer F et al. Practicability of Nitrogen Multiple-Breath Washout Measurements in a Pediatric Cystic Fibrosis Outpatient Setting. Pediatric Pulmonology 2013; 48:739–746
[5] Oude Engberink et al. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. Eur Respir J 2017; 50: 1700433 https://doi.org/10.1183/13993003.00433-2017

account for these data if these four patients had any post-baseline data available were consistent with the primary analyses that excluded subjects with missing baseline.

Regarding the post-baseline data, it is acknowledged that all reasonable efforts to collect data given the COVID-19 pandemic were made. However, despite the effort, the collection of data on the endpoints at week 16 and week 24 was hampered by the pandemic. At week 16, e.g. ppFEV1 data were available for 29 patients and at week 24 data were only available for 15 patients under the usual follow-up schedule and for 24 patients when patients who participated in an unscheduled visit were included. The inclusion of patient data from unscheduled visits is likely to introduce bias into the estimate of the outcome as these data may be from healthier, lower-risk patients. It is also noted that some of these data were collected much later than 24 weeks.

Based on the accumulating evidence from previous studies, it is accepted that the effect of a modulator can already be observed around 4 to 8 weeks following treatment. At the request of the CHMP, rather than using additional analyses to try to reach a reasonable estimate of the within-group change through week 24, additional analyses excluding all Week 16 and 24 data were performed, that were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and that demonstrated a robust and clinically meaningful improvements. Because of the many missing data and the potential bias for the 24 weeks results, it was considered by CHMP that both the results for 12 weeks and 24 weeks needed to be included in the SmPC section 5.1.

Some patients also had missing data up to week 12. Given the very high reported rate of study and treatment completion, it is not immediately clear why these data were missing. For the sensitivity analysis, given the way the missing categories were defined, only 2 participants would have been allocated to the missing category 1, for which it was assumed that the mean response at a particular timepoint was the lower quartile of the observed data. The other participants had missing data imputed based on the mean of the observed data. Therefore, this sensitivity analysis is essentially making the same (MAR) assumptions as the MMRM model. Because the efficacy endpoints are secondary to the PK results and the lack of a control group, this limits the options for further sensitivity analysis and additional sensitivity analyses were not requested. Instead, at the request of the CHMP, to support the analyses provided at week 12, the Applicant provided the missing data patterns for the FAS population up to and including week 12, and where available, provided justification for these missing data, considered acceptable. Given the strength of the effect in both the week 12 and week 24 results, and the low number of "Category 1" discontinuations, no further analyses are considered required by CHMP.

Upon request from CHMP, sub-analyses for the F/F and F/MF patient groups were presented by the MAH. The populations F/F and F/MF were comparably represented in the overall population. The results of both populations are generally in line with the overall group. The improvements were in both groups clinically meaningful.

Indication

The investigated population of patients with F/MF genotypes or F/F genotype is tighter than the population for which in a recent line extension Kaftrio was granted a positive opinion by the CHMP (EMEA/H/C//005269/II/0001 approved on 26 April 2021). In this procedure, the indication was broadened to include CF patients from the age of 12 years with F/RF and F/G mutation to the already registered CF patients with F/F and F/MF mutations, resulting in the current indication of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene.

Therefore, the CHMP requested the MAH to provide justification to discuss possible broadening of the indication in patients from 6 years of age, in patients with MF mutations to patients with F/Any mutations.

Principle of Extrapolation

The expansion of the indication to children 6 through 11 years old is based on the principle of partial extrapolation from adult and adolescents to paediatric patients as has been accepted for the indication expansion of Symkevi (TEZ/IVA) (EMEA/H/C/004682/X/0015).

Consistent with the principles described in ICH E11, 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.

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.

In conclusion, the further extrapolation to CF subjects 6 through 11 years of age with F/G and F/RF mutation is acceptable based on the same arguments as for the CF patients with F/F and F/MF mutations in combination with the additional evidence of the statistically significant benefits of ELX/TEZ/IVA over previously available CFTR modulators (IVA or TEZ/IVA) in CF subjects ≥ 12 years of age with F/RF and F/G genotypes. (reference to EMEA/H/C//005269/II/0001 approved on 26 April 2021).

2.6.4. Conclusions on clinical efficacy

The results in the efficacy endpoints generally support a benefit in the investigated population. However, the results are impacted by missing data because of the COVID-19 pandemic and related restrictions during the later stage of the study. As known from previous trials, by week 12, steady and reliable results can already be observed. The analyses excluding all Week 16 and 24 data, were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and demonstrated a robust and clinically meaningful improvements.

The extension of the indication to children 6 through 11 years old who are heterozygous for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype) is based on the principle of partial extrapolation from adult and adolescents to paediatric patients. The principle of partial extrapolation can be considered justified in CF for the CFTR therapies, because of the similar underlying genetic, and molecular aetiology of CF of children and patients ≥ 12 years. Children and adults share the same disease characteristics although they are more severe in adults because of the progression of the symptoms. Efficacy is a secondary objective in this application. The extrapolation is based on comparable exposure and safety.

Further extrapolation of efficacy data in CF patients with F/F and F/MF mutations to CF subjects 6 through 11 years of age with F/G and F/RF mutation is acceptable considering also the additional

evidence of the statistically significant benefits of ELX/TEZ/IVA over previously available CFTR modulators (IVA or TEZ/IVA) in CF subjects ≥ 12 years of age with F/RF and F/G genotypes.

The extension of indication is acceptable by CHMP as described below:

Kaftrio is 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 (see section 5.1).

2.7. Clinical safety

The clinical safety of ELX/TEZ/IVA has previously assessed in the clinical trial in patients aged ≥ 12 years.

The main clinical safety database to support the application in children aged 6-11 years includes the safety data from Study 106, a Phase 3, single-arm, multi-centre study conducted in 2 parts (Parts A and B) to evaluate the pharmacokinetic (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are homozygous for F508del (F/F genotype) or heterozygous for F508del and a minimal function (MF) mutation (F/MF genotypes).

Only the results of paediatric study VX18-445-106 are reported. No integrated safety report has been provided including the comparison with the adult/adolescent safety database.

Patient exposure

Study VX18-445-106 consists of two parts. In Part A of study VX445-106, all patients received the same dose of ELX/TEZ/IVA. In part B, the patients received a weight-based posology based on the provided PK data of Part A.

Part A

A total of 16 subjects received at least 1 dose of the study drug in the Part A treatment period. The mean (SD) exposure was 14.9 (0.68) days (Table 24).

Part B

A total of 66 subjects received at least 1 dose of the study drug in the Part B Treatment Period, with a mean (SD) exposure of 23.8 (3.0) weeks (Table 25).

Table 24 Summary of exposure (Safety Set, Part A)

	ELX/TEZ/IVA N = 16
Total exposure (patient weeks)	34.1
Exposure duration (days)	
n	16
Mean (SD)	14.9 (0.68)
Median	15.0
Min, max	14, 16
Exposure duration by interval, n (%)	
≤2 days	0
>2 to ≤4 days	0
>4 to ≤8 days	0
>8 to ≤15 days	13 (81.3)
>15 days	3 (18.8)

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 (days) = (last dose date – first dose date + 1), regardless of study drug interruption. Duration of study drug exposure (weeks) = duration of study drug exposure (days)/7; 1 week = 7 days.

Table 25 Summary of exposure (Safety Set, Part B)

	ELX/TEZ/IVA N = 66
Total exposure (patient weeks)	1570.4
Total exposure (patient years)	32.7
Exposure duration (weeks)	
n	66
Mean (SD)	23.8 (3.0)
Median	24.1
Min, max	0.1, 24.9
Exposure duration by interval, n (%)	
≤15 days	1 (1.5)
>15 days to ≤20 weeks	0
>20 to ≤24 weeks	27 (40.9)
>24 weeks	38 (57.6)

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 – first dose date + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = (last dose date – first dose date + 1)/336, regardless of study drug interruption; 336 days = 48 weeks.

Adverse events

Adverse events part A and part B

The AEs generated in study VX-445-106 are briefly summarized in Table 24. During the study, there were no deaths reported. A total of one patient experienced serious AEs (pneumonia, metapneumovirus infection, and rhinovirus infection), and one patient experienced an AE (rash erythematous) that led to discontinuation. Two patients experienced AEs (one patient rash maculo-papular; one patient diarrhea, pyrexia, and vomiting), that led to interruption of treatment (Table 26).

Table 26 Overview of the AE's (safety set, part A and Part B

Category	Part A N=16 n (%)	Part B N = 66 n (%)
Number of AEs (total)	44	341
Subjects with any AEs	12 (75.0)	65 (98.5)
Subjects with AEs by strongest relationship		
Not related	1 (6.3)	16 (24.2)
Unlikely related	2 (12.5)	16 (24.2)
Possibly related	9 (56.3)	29 (43.9)
Related	0	4 (6.1)
Subjects with AEs by maximum severity		
Mild	10 (62.5)	36 (54.5)
Moderate	1 (6.3)	28 (42.4)
Severe	1 (6.3)	1 (1.5)
Life-threatening	0	0
Missing	0	0
Subjects with AEs leading to study drug discontinuation	0	1 (1.5)
Subjects with AEs leading to study drug interruption	1 (6.3)	1 (1.5)
Subjects with Grade 3/4 AEs	1 (6.3)	1 (1.5)
Subjects with SAEs	0	1 (1.5)
Subjects with AEs leading to death	0	0
Subjects with related AEs[a]	9 (56.3)	33 (50.0)
Subjects with related SAEa	0	0

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

Adverse events Part A

In part A, a total of n=12 (75%) had at least one AE. A total of n=1 (6.3%) subject had a severe AE.

No subjects discontinued study drug due to AEs, and 1 (6.3%) subject interrupted study drug due to rash maculo-papular, unlikely related to medication (Table 26).

Adverse events that occurred in ≥ 2 patients were cough (n=5, 31.3%), rash (n=3,18.8%), sputum increased (n=3, 18.8%), nasal congestion (n=2, 12.5%) and productive cough (n=2, 12.5%). (Table 27)

Treatment related adverse events occurred in n=9 patients. The most frequently reported treatment related adverse event were sputum increased (n=3, 18.8%), cough (n=2, 12.5%) and productive cough (n=2, 12.5 %) (*Table 28*)

Table 27 Adverse Events Occurring in ≥2 Subjects by System Organ Class and Preferred Term (Study 106 Part A, Safety Set)

System Organ Class Preferred Term	ELX/TEZ/IVA N = 16 n (%)
Subjects with any AEs	12 (75.0)
Respiratory, thoracic and mediastinaldisorders	**10 (62.5)**
Cough	5 (31.3)
Sputum increased	3 (18.8)
Nasal congestion	2 (12.5)
Productive cough	2 (12.5)
Skin and subcutaneous tissue disorders	**5 (31.3)**
Rash	3 (18.8)

Source: Study 106 CSR/Table 14.3.1.2a
AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Note: A subject with multiple events within a category was counted only once in that category

Table 28 Treatment-related AEs by System Organ Class and Preferred Term - Part A Safety Set

System Organ Class Preferred Term	VX-445/TEZ/IVA N = 16 n (%)
Subjects with any treatment-related AEs	**9 (56.3)**
Respiratory, thoracic and mediastinal disorders	**6 (37.5)**
Sputum increased	3 (18.8)
Cough	2 (12.5)
Productive cough	2 (12.5)
Respiration abnormal	1 (6.3)
Investigations	**2 (12.5)**
Blood alkaline phosphatase increased	1 (6.3)
Transaminases increased	1 (6.3)
Skin and subcutaneous tissue disorders	**2 (12.5)**
Rash	2 (12.5)
Gastrointestinal disorders	**1 (6.3)**
Abdominal pain upper	1 (6.3)
General disorders and administration site conditions	1 (6.3)
Chest pain	1 (6.3)

AE: adverse event; ALT: alanine transaminase; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor
Notes: AEs were coded using MedDRA version 21.1. 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 System Organ Class, and by PT within each System Organ Class.

Adverse events Part B

In part B, a total of sixty-five (98.5%) subjects had at least 1 AE. Most subjects had AEs that were mild or moderate in severity; 1 (1.5%) subject had severe AEs. One (1.5%) subject each had SAEs, discontinued study drug due to an AE, and interrupted study drug due to AEs (Table 26).

The most frequently reported adverse events were cough (n=28, 42.4%), headache (n=16 (24.2%) and pyrexia (n=14 (21.2 %).
Additional AEs reported with a frequency > 10% were oropharyngeal pain (n=12, 18.2%), upper respiratory tract infection (n=11, 6.7%), nasal congestion (n=10, 15.2%), abdominal pain (n=8, 12.1%), rash (n=8, 12.1%), rhinorrhoea (n=8, 12.1%), viral upper respiratory tract infection (n=8, 12.1%), ALT increased (n=7, 10.6%), diarrhoea (n=7, 10.6%), influenza (n=7, 10.6%), and vomiting (n=7, 10.6%) (*Table 29*)

Treatment-related adverse events were reported in a total of n=33 patients (50%). The most frequently reported treatment-related adverse event by PT was abdominal pain (n=6 (9.1%), followed by alanine aminotransferase increase (n=5, 7.6%), rash n=4 (6.1%) and headache n= 4 (6.1%) (Table 30)

Table 29 Adverse Events Occurring in ≥3 Subjects by System Organ Class and Preferred Term (Study 106 Part B, Safety Set)

System Organ Class **Preferred term**	**ELX/TEZ/IVA** **n=66** **n (%)**
Subjects with adverse events	**65 (98.5)**
Respiratory, thoracic and mediastinal disorders	**48 (72.7)**
Cough	28 (42.4)
Oropharyngeal pain	12 (18.2)
Nasal congestion	10 (15.2)
Rhinorrhoea	8 (12.1)
Productive cough	5 (7.6)
Sputum increased	3 (4.5)
Wheezing	3 (4.5)
Infections and infestations	**34 (51.5)**
Upper respiratory tract infection	11 (16.7)
Viral upper respiratory tract infection	8 (12.1)
Influenza	7 (10.6)
Ear infection	4 (6.1)
Conjunctivitis	3 (4.5)
Infective pulmonary exacerbation of cystic fibrosis	3 (4.5)
Gastrointestinal disorders	**27 (40.9)**
Abdominal pain	8 (12.1)
Diarrhoea	7 (10.6)
Vomiting	7 (10.6)
Abdominal pain upper	5 (7.6)
Constipation	4 (6.1)
General disorders and administration site conditions	**19 (28.8)**
Pyrexia	14 (21.2)
Fatigue	5 (7.6)
Skin and subcutaneous tissue disorders	**19 (28.8)**
Rash	8 (12.1)
Rash erythematous	3 (4.5)

Investigations	**16 (24.2)**
Alanine aminotransferase increased	7 (10.6)
Nervous system disorders	**16 (24.2)**
Headache	16 (24.2)
Injury, poisoning and procedural complications	**7 (10.6)**
Psychiatric disorders	**7 (10.6)**
Ear and labyrinth disorders	**5 (7.6)**
Musculoskeletal and connective tissue disorders	**3 (4.5)**

Source: Study 106 CSR/Table 14.3.1.2b
AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size;TEZ: tezacaftor
Note: A subject with multiple events within a category was counted only once in that category.

Table 30 Treatment-related adverse events by SOC and PT-safety set part B

System Organ Class Preferred Term	ELX/TEZ/IVA N = 66 n (%)
Subjects with any related TEAEs	**33 (50.0)**
Gastrointestinal disorders	**12 (18.2)**
Abdominal pain	6 (9.1)
Abdominal pain upper	2 (3.0)
Nausea	2 (3.0)
Diarrhoea	1 (1.5)
Post-tussive vomiting	1 (1.5)
Vomiting	1 (1.5)
Respiratory, thoracic and mediastinal disorders	**11 (16.7)**
Cough	3 (4.5)
Sputum increased	3 (4.5)
Productive cough	2 (3.0)
Bronchospasm	1 (1.5)
Haemoptysis	1 (1.5)
Nasal congestion	1 (1.5)
Pleuritic pain	1 (1.5)
Rhinorrhoea	1 (1.5)
Sputum discoloured	1 (1.5)
Wheezing	1 (1.5)
Skin and subcutaneous tissue disorders	**8 (12.1)**
Rash	4 (6.1)
Rash erythematous	2 (3.0)
Rash maculo-papular	2 (3.0)
Rash papular	1 (1.5)
Investigations	**7 (10.6**)
Alanine aminotransferase increased	5 (7.6)
Aspartate aminotransferase increased	1 (1.5)
Blood bilirubin increased	1 (1.5)
Blood creatine phosphokinase increased	1 (1.5)

Nervous system disorders	**4 (6.1)**
Headache	4 (6.1)
Psychiatric disorders	**3 (4.5)**
Aggression	1 (1.5)
Anxiety	1 (1.5)
Depressed mood	1 (1.5)
General disorders and administration site conditions	**1 (1.5)**
Fatigue	1 (1.5)
Injury, poisoning and procedural complications	**1 (1.5)**
Accidental overdose	1 (1.5)

MedDRA version 23.0.
A subject with multiple events within a category is counted only once in that category.
Table is sorted in descending order of frequency of the ELX/TEZ/IVA column by System Organ Class, and by Preferred Term within each System Organ Class. When summarizing number of subjects with related TEAEs, TEAEs with relationship of related, possibly related, and missing are counted.

Adverse events of special interest

Adverse events of special interests were AEs of elevated transaminases and AEs, rash and ocular lens opacity.

- Elevated Transaminase Events

In part A, one subject (1/16, 6.3%) with a history of liver function test increased had a nonserious AE of transaminases increased 1 day after the last dose of study drug treatment; the AE was considered by the investigator to be mild in severity and possibly related to study drug

In Part B, most patients had ALT and AST levels that remained in the normal range. Seven (10.6%) subjects had elevated transaminase events. All these events were mild or moderate in severity. None of the events were serious or led to treatment discontinuation or interruption.

- Rash Events

In part A, five subjects (5/16, 31.3%) had a total of 6 rash events. One subject had an AE of maculo-papular rash that led to study drug interruption.

In part B, sixteen (24.2%) subjects had at least 1 rash event. One subject had a rash event of moderate severity that led to treatment discontinuation.

- Ophthalmologic examinations (Part B).

Ophthalmologic examination occurred at screening and at the end of treatment. No subjects had AEs of cataract or lens opacity.

Not all patients of part B underwent a post-treatment ophthalmologic examination because of the COVID pandemic. The number of patients that underwent ophthalmologic examination before and after treatment is not reported.

Serious adverse events and deaths

During the study VX 445-106, one SAE occurred in Part B of the study in one subject. The event was assessed as moderate in severity and unlikely related to study drug, did not lead to study treatment discontinuation or interruption, and resolved. This event is considered unlikely to be related to treatment.

No deaths occurred during the study.

Laboratory findings

Chemistry

Part A

In part A, there were no trends observed in the Liver Function Test and non-Liver Function Test chemistry parameters. No subjects had ALT or AST >3 × ULN in the TE Period, nor total bilirubin >2 × ULN.

Part B

In part B, most subjects had ALT and AST values that remained within the normal range. Mean concentrations of LFT parameters were variable, with no consistent trends over time in ALT, AST, ALP, or GGT values

Seven (10.6%) subjects had ALT or AST >3 × ULN, and 1 (1.5%) subject had ALT or AST >5 × ULN; no subjects had ALT or AST >8 × ULN. No subject had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN (Table 31)

Most subjects had bilirubin values that remained within the normal range (Table 31); One (1.5%) subject had 2 AEs of blood bilirubin increased, neither of which were serious or led to treatment discontinuation or interruption, one of which was considered possibly related to treatment.

No subjects had AEs of GGT increased, or ALP increased, although the lab assessment showed elevations of GGT and ALP above threshold values in n=8 and n=19 patients respectively (Table 31).

Table 31 Threshold analyses of LFT chemistry parameters during the TE period (Part B safety set)

Post baseline threshold analysis criteria	Elx/Tez/Iva N=66
AST (U/L)	
>ULN to ≤3 × ULN	23 (34.8)
>3 × ULN	0
ALT (U/L) or AST (U/L)	
(ALT>ULN to ≤3 × ULN) or (AST>ULN to ≤3 × ULN)	44 (66.7)
(ALT>3 × ULN) or (AST>3 × ULN)	7 (10.6)
(ALT>5 × ULN) or (AST>5 × ULN)	1 (1.5)
Total bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	7 (10.6)
>1.5 × to ≤2 × ULN	4 (6.1)
Direct bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	10 (15.2)
Indirect bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	8 (12.3)
>1.5 × to ≤2 × ULN	1 (1.5)
>2 × to ≤3 × ULN	3 (4.6)
(**ALT or AST) and TBILI**	
(ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN	0
Lipase ALP (U/L)	
>ULN to ≤1.5 × ULN	17 (25.8)
>1.5 × to ≤2.5 × ULN	2 (3.0)

GGT (U/L)	
>ULN to ≤2.5 × ULN	7 (10.6)
>2.5 × to ≤5 × ULN	1 (1.5)

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

Creatine Kinase

The mean CK concentration was variable over time; overall, increases from baseline were observed. The mean (SD) increase in CK ranged from 30.2 (32.7) U/L at Week 12 to 53.4 (68.8) U/L at Week 24

Most subjects had CK levels that remained within the normal range; a total of n=21 (31.8%) had CK levels > ULN to ≤ 2.5 ULN, N= 4 (6.1%) subjects had CK levels >2.5 × ULN, and no subjects had CK levels >5 × ULN.

AEs of CK elevation occurred in 2 (3.0%) subjects, in one patient it was considered to be related to medication (Table 30). Neither AE was serious or led to study drug discontinuation or interruption, and both AEs resolved without treatment.

Haematology

Minor decreases from baseline in mean platelets, leukocytes, and neutrophils were observed: mean values of these parameters were not below the respective normal range at any assessed time point.

Two subjects had mild AEs related to haematology findings (1 subject with leukopenia, 1 subject with white blood cell count increased); none of the AEs were serious or led to treatment discontinuation or interruption.

Coagulopathy

There were no trends observed in coagulation parameters. Three subjects had AEs related to coagulation findings considered not to be related to treatment; none of the AEs were serious or led to treatment discontinuation or interruption.

Vital signs

All patients in part A, and a total of n=33 patients in part B (50% of safety data set) completed the safety measurements (blood pressure, ECG) at the end of the treatment period.

Decreases from baseline in pulse rate were observed. The mean (SD) decrease in pulse rate ranged from -1.8 (10.9) bpm at Week 16 to -4.8 (13.6) bpm at Week 4. There were no other trends observed in other vital signs parameters, including BP. No subjects had AEs related to Blood pressure or pulse rate findings.

One subject had an AE of defect conduction intraventricular, which was nonserious, not related to study drug, and did not lead to treatment discontinuation or interruption; no other subjects had AEs related to ECG findings or relevant cardiac disorders.

Discontinuation due to AES

All patients in part A completed the study.

One patient (n=1, 1.5%) in part B discontinued prematurely due to an erythematous rash of moderate severity that was considered related to treatment. The study drug was withdrawn, and a single dose of cetirizine was administered. The event resolved the next day.

Treatment interruptions due to AEs

The treatment was temporarily interrupted in two patients, one in part A and one in part B.

In part A, one (6.3%) subject had an AE of rash maculo-papular of mild intensity that led to treatment interruption. The AE resolved; the subject resumed ELX/TEZ/IVA and also completed dosing. The AE was considered unrelated to treatment.

In part B, the treatment was temporarily interrupted in one patient because of AEs, unlikely to be related to medication. The dose of ivacaftor was interrupted for one day and the event resolved.

Comparisons of the safety profile in patients aged ≥ 12 and patients aged 6-11 years old

In response to the LoQ, the applicant provided a comparison of the adverse events observed in the paediatric population (children aged 6-11 years) and the patients aged ≥ 12 years

The safety data for the paediatric population is obtained in study 106 part B. The safety for the patients aged ≥ 12 years is obtained in study 102. As both studies were of the same duration, the comparison of the AE incidence data is provided.

Comparisons overall safety profile

The overall adverse event profile by number of AE's, treatment related AE, discontinuations etc. show a comparable number of events are comparable between the paediatric population and the patients aged ≥ 12 years (Table 32).

Table 32 Overview of Adverse Events (Study 102 Safety Set, Study 106 Part B Safety Set), Through 24 Weeks of Treatment

	Study 102		**Study 106 Part B**
	Placebo N = 201n (%)	**ELX/TEZ/IV AN = 202 n (%)**	**ELX/TEZ/IV AN = 66 n (%)**
Number of AEs (total)	1287	1098	341
Subjects with any AEs	193 (96.0)	188 (93.1)	65 (98.5)
Subjects with AEs by strongest relationship			
Not related	83 (41.3)	53 (26.2)	16 (24.2)
Unlikely related	58 (28.9)	39 (19.3)	16 (24.2)
Possibly related	46 (22.9)	86 (42.6)	29 (43.9)
Related	6 (3.0)	10 (5.0)	4 (6.1)
Subjects with AEs by maximum severity			
Mild	53 (26.4)	67 (33.2)	36 (54.5)
Moderate	125 (62.2)	102 (50.5)	28 (42.4)
Severe	14 (7.0)	19 (9.4)	1 (1.5)
Life-threatening	1 (0.5)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0(0)
Subjects with AEs leading to study drug discontinuation	0 (0)	2 (1.0)	1 (1.5)

Subjects with AEs leading to study drug interruption	10 (5.0)	19 (9.4)	1 (1.5)
Subjects with Grade 3/4 AEs	15 (7.5)	19 (9.4)	1 (1.5)
Subjects with related AEs[a]	52 (25.9)	96 (47.5)	33 (50.0)
Subjects with SAEs	42 (20.9)	28 (13.9)	1 (1.5)
Subjects with related SAEs[a]	2 (1.0)	6 (3.0)	0 (0)
Subjects with AEs leading to death	0 (0)	0 (0)	0 (0)

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.

Adverse event irrespective of causal relation ship

In addition, to the overall adverse event profile, also a comparison of the AE by SoC and PT were presented, irrespective of the causal relationship

In the paediatric population, the following SoC showed a higher frequency (≥ 5%) compared to the ≥12 year old population i.e.:

- SOC Respiratory, thoracic and mediastinal i.e. 73% vs 50%
- SOC General disorders and administration site conditions 29% vs 16%

In the **SOC Respiratory, thoracic and mediastinal adverse events**, the largest difference in the AE (PT) is shown by the PT cough 42% vs 17%, nasal congestion (15% vs 9%), oropharyngeal pain (~ 18% vs 10 %) and rhinorrhoea (~12% vs 8%).

In the **SOC General disorders and administration site conditions**, the differences between the paediatric and ≥12 year old population (29% vs 16%) is driven by the higher reported frequency of pyrexia (21 % vs, 8%). In the paediatric population, none of the adverse events were considered being related to study medication.

The **SOC Investigations** showed a higher reported frequency of the PT blood creatine phosphokinase increase in the population aged ≥ 12 years (9.4% vs 3%) compared the paediatric population

Table 33 Adverse Events by System Organ Class and Preferred Term in Study 102(Safety Set), and Study 106 Part B (Safety Set) ;
PT with a difference > 5% between study 102 and 106, of referring to an AE of specific interest

System Organ Class PreferredTerm	Placebo N = 201 n (%)	Study 102 ELX/TEZ/IVA N = 202 n (%)	Study 106 Part B ELX/TEZ/IVA N = 66 n (%)
Subjects with any AEs	**193(96.0)**	**188 (93.1)**	**65 (98.5)**
Infections and infestations	**145(72.1)**	**121 (59.9)**	**34 (51.5)**
Respiratory, thoracic and mediastinal	**129(64.2)**	**100 (49.5)**	**48 (72.7)**
Cough	77 (38.3)	34 (16.8)	28 (42.4)
Oropharyngeal pain	25(12.4)	20 (9.9)	12 (18.2)
Nasal congestion	15 (7.5)	19 (9.4)	10 (15.2)
Rhinorrhoea	6 (3.0)	17 (8.4)	8 (12.1)
Gastrointestinal disorders	**58(28.9)**	**78 (38.6)**	**27 (40.9)**
Abdominal pain	12 (6.0)	20 (9.9)	8 (12.1)
Vomiting	10 (5.0)	12 (5.9)	7 (10.6)
Abdominal pain upper	6 (3.0)	9 (4.5)	5 (7.6)
Investigations	**71(35.3)**	**66 (32.7)**	**16 (24.2)**
Alanine aminotransferase increased	7 (3.5)	20 (9.9)	7 (10.6)
Aspartate aminotransferase increased	4 (2.0)	19 (9.4)	2 (3.0)
Blood creatine phosphokinase increased	9 (4.5)	19 (9.4)	2 (3.0)
Blood bilirubin increased	2 (1.0)	10 (5.0)	1 (1.5)
Nervous system disorders	**40(19.9)**	**50 (24.8)**	**16 (24.2)**
Skin and subcutaneous tissue disorders	**29(14.4)**	**46 (22.8)**	**19 (28.8)**
Rash	9 (4.5)	18 (8.9)	8 (12.1)
General disorders and administration site conditions	**55 (27.4)**	**33 (16.3)**	**19 (28.8)**
Pyrexia	19 (9.5)	17 (8.4)	14 (21.2)
Musculoskeletal and connective tissue	**30(14.9)**	**27 (13.4)**	**3 (4.5)**
Injury, poisoning and procedural complications	**8 (4.0)**	**20 (9.9)**	**7 (10.6)**
Psychiatric disorders	**11 (5.5)**	**13 (6.4)**	**7 (10.6)**

Eye disorders	**10 (5.0)**	**8 (4.0)**	**1 (1.5)**
Lenticular opacities	0 (0)	1 (0.5)	0
Ear and labyrinth disorders	**4 (2.0)**	**7 (3.5)**	**5 (7.6)**
Hepatobiliary disorders	**2 (1.0)**	**7 (3.5)**	**0**
Blood and lymphatic system disorders	**5 (2.5)**	**6 (3.0)**	**1 (1.5)**
Cardiac disorders	**2 (1.0)**	**6 (3.0)**	**1 (1.5)**
Renal and urinary disorders	**10(5.0)**	**5 (2.5)**	**0**
Immune system disorders	**4 (2.0)**	**4 (2.0)**	**1 (1.5)**
Vascular disorders	**3 (1.5)**	**3 (1.5)**	**0**
Congenital, familial and genetic disorders	**3 (1.5)**	**0**	**0**
Endocrine disorders	**1 (0.5)**	**0**	**0**
Product issues	**2 (1.0)**	**0**	**0**

Table made by assessor based on data provided by the applicant. The patients in study 102 are aged ≥ 12 years, in study 106 aged 6-11 years.

Differences in frequency of drug related adverse events

Upon request, on overview of the drug related adverse event was provided.

In the paediatric population, most drug related AE's were reported In the SOC Gastrointestinal disorders (18.2%), followed by the SOC Respiratory, Thoracic and Mediastinal disorders (16.7%), SOC Skin and subcutaneous tissue disorders (12.1%) and SOC investigations (10.6%).

For the ≥12 year old population, this frequency was SOC Respiratory, Thoracic and Mediastinal disorders (14.4%), SOC investigations (12.9%), the SOC Gastrointestinal disorders (10.9%), and Skin and subcutaneous tissue disorders (8.9 %).

Regarding the **SOC investigations**, the paediatric population reported a higher frequency of treatment related ALAT increased compared with the ≥12 year old population (7.6 %vs 5.9 %)) , while the PT (ASAT increased 1.5 vs 5.4.%) and blood bilirubin increase (1.5% vs 3.0 %) were lower than reported in the ≥12 year old population.

Table 34 Drug Related Adverse Events with by System Organ Class and Preferred Term in Study 102 (Safety Set), and Study 106 Part B (Safety Set),

System Organ Class Preferred Term	Study 102 Placebo N = 201 n (%)	Study 102 ELX/TEZ/IVA N = 202 n (%)	Study 106 Part B ELX/TEZ/IVA N = 66 n (%)
Subjects with any related AEs	**52 (25.9)**	**96 (47.5)**	**33 (50.0)**
Infections and infestations	**5 (2.5)**	**2 (1.0)**	**0 (0)**
Respiratory, thoracic and mediastinal disorders	**25 (12.4)**	**29 (14.4)**	**11 (16.7)**
Sputum increased	10 (5.0)	14 (6.9)	3 (4.5)
Cough	13 (6.5)	7 (3.5)	3 (4.5)
Productive cough	5 (2.5)	7 (3.5)	2 (3.0)
Haemoptysis	0 (0)	4 (2.0)	1 (1.5)
Respiration abnormal	1 (0.5)	4 (2.0)	0 (0)
Rhinorrhoea	3 (1.5)	4 (2.0)	1 (1.5)
Wheezing	0 (0)	1 (0.5)	1 (1.5)
Nasal congestion	4 (2.0)	0 (0)	1 (1.5)
Sputum discoloured	1 (0.5)	0 (0)	1 (1.5)
Bronchospasm	0 (0)	0 (0)	1 (1.5)
Pleuritic pain	0 (0)	0 (0)	1 (1.5)
Gastrointestinal disorders	**12 (6.0)**	**22 (10.9)**	**12 (18.2)**
Abdominal pain	1 (0.5)	2 (1.0)	6 (9.1)
Abdominal pain upper	3 (1.5)	5 (2.5)	2 (3.0)
Nausea	3 (1.5)	4 (2.0)	2 (3.0)
Diarrhea	4 (2.0)	4 (2.0)	1 (1.5)
Vomiting	0 (0)	2 (1.0)	1 (1.5)
Post-tussive vomiting	0 (0)	0 (0)	1 (1.5)
Investigations	**9 (4.5)**	**26 (12.9)**	**7 (10.6)**
Alanine aminotransferase increased	1 (0.5)	12 (5.9)	5 (7.6)
Aspartate aminotransferase increased	0 (0)	11 (5.4)	1 (1.5)
Blood creatine phosphokinase increased	2 (1.0)	10 (5.0)	1 (1.5)
Blood bilirubin increased	0 (0)	6 (3.0)	1 (1.5)
Nervous system disorders	**10 (5.0)**	**11 (5.4)**	**4 (6.1)**
Headache	8 (4.0)	9 (4.5)	4 (6.1)
Metabolism and nutrition disorders	**3 (1.5)**	**6 (3.0)**	**0 (0)**
Skin and subcutaneous tissue disorders	**7 (3.5)**	**18 (8.9)**	**8 (12.1)**
Rash	3 (1.5)	11 (5.4)	4 (6.1)
Rash erythematous	1 (0.5)	0 (0)	2 (3.0)

Rash maculo-papular	0 (0)	0 (0)	2 (3.0)
Rash papular	0 (0)	0 (0)	1 (1.5)
Pruritis	0 (0)	4 (2.0)	0 (0)
Rash generalized	0 (0)	2 (1.0)	0 (0)
General disorders and administration site conditions	**7 (3.5)**	**4 (2.0)**	**1 (1.5)**
Fatigue	3 (1.5)	3 (1.5)	1 (1.5)
Musculoskeletal and connective tissue	**2 (1.0)**	**6 (3.0)**	**0 (0)**
Injury, poisoning and procedural complications	**0** (0)	**0 (0)**	**1 (1.5)**
Accidental overdose	0 (0)	0 (0)	1 (1.5)
Psychiatric disorders	**2 (1.0)**	**3 (1.5)**	**3 (4.5)**
Anxiety	0 (0)	0 (0)	1 (1.5)
Depressed mood	0 (0)	0 (0)	1 (1.5)
Aggression	0 (0)	0 (0)	1 (1.5)

The patients in study 102 are aged ≥ 12 years, in study 106 aged 6-11 years. Selection of the SoC and PT is based on the drug reported AE in study 106B and the incidence of n≥ 2 in study 102.

Adverse event of Specific Interest

Adverse events of special interests were AEs of elevated transaminases and AEs, rash and ocular lens opacity. As none of the paediatric patient had an AEsi of ocular opacity, this will not be discussed further here.

AESI transaminase elevation

A cross study comparison of the AESi of transaminase elevation is provide in

Table 35. The data show, that the occurrence of the AEsi (ALAT or ASAT ≥ 3 × ULN) were slightly higher in the paediatic population (10.6%) compared with the patients ≥ 12 years (7.9%). None of the paediatric patients reported ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN (Table 35).

Table 35 Analysis of Transaminase Elevations During the Treatment-emergent Period:

	Study 102 Placebo N=201	Study 102 ELX/TEZ/IVA N=202	Study 106 ELX/TEZ/IVA N=66
ALT (U/L) or AST (U/L) cumulative			
(ALT>3 × ULN) or (AST>3 × ULN)	11 (5.5)	16 (7.9)	7 (10.6)
(ALT>5 × ULN) or (AST>5 × ULN)	3 (1.5)	5 (2.5)	1 (1.5)
(**ALT or AST) and TBILI**			
(ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN	0	2 (1.0)	0

Source: table 49 EPAR Kaftrio, table overview.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; TEZ: tezacaftor; ULN: upper limit of normal
Table made by assessor The patients in study 102 are aged ⩾ 12 years, in study 106 aged 6-11 years

AESI Rash

The generalised AEsi Rash included the PT Rash, PT Rash generalised, Rash macular, Rash pruritic, Rash erythematous, Rash maculo-papular and Rash papular.

The paediatric population showed an approximately 2 times higher reported frequency reported than in the ≥ 12-year-old population for both AEsi-Rash-irrespective-of-causality (24.2% vs 10.9%), and the AEsi-Rash-treatment-related (12.1% vs 6.9%).

Postmarketing experience

As of 20 October 2020, it is estimated that 23,556 patients (representing 13,467.1 person-years) have been exposed to ELX/TEZ/IVA.

In April 2021, the applicant submitted a type II variation to update the Summary of Product Characteristics and Package Leaflet to include hepatic safety data for Kaftrio (EMEA/H/C/005269) (sequence 0031) and Kalydeco (EMEA/H/C/002494). This assessment was performed in parallel of this application.

The request for the update for the SmPC was initiated by Vertex post-marketing pharmacovigilance. The post-marketing pharmacovigilance showed 3 cases of liver injury characterized by concomitant transaminase (ALT and AST) elevations >3 × ULN and total bilirubin elevations >2 × ULN were reported, including 1 case of liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension.

2.7.1. Discussion on clinical safety

The main safety data set to support the application in children aged 6-11 is provided by part B of the single-arm, open-label study VX18-445-106, where 66 patients were treated for 24 weeks.

The provided safety data set to support the application is considered limited to support a substance intended for chronic use. Also, because of COVID pandemic, not all patients underwent a full safety measurement after completion of the study. In addition to its limited data set size and treatment duration, the safety data is collected in an uncontrolled, open-label study, in which the contribution from the longer disease duration is hard to distinguish from the longer drug exposure. Therefore, a cross study comparisons were provided upon request from the CHMP of the safety profile obtained in the paediatric population and the patients aged ≥ 12 years to support the safety profile obtained in the paediatric population.

Overall, the provided paediatric safety set showed that the treatment appears to be well tolerated up to 24 weeks in the paediatric population, as shown by the reported low number of serious adverse events (1.5%), treatment interruptions (1.5%) and treatment discontinuations due to AE (1.5%). Similarly, to the patients aged ≥ 12 years, the treatment appears well-tolerated and the safety profile is overall consistent with the known safety profile of Kaftrio.

There is an open-label extension roll over study 107 currently ongoing which should provide an opportunity to collect the missing safety data. This study will provide more prolonged safety data (up to 96 weeks), but the included paediatric patients number will still be limited (n=64). The data will need to be submitted once the study is completed.

Adverse events, serious adverse events and deaths

Nearly all paediatric patients (98.5%) experienced an adverse event. The reported adverse events were most likely related to the common manifestation of CF disease or common illnesses.

About 50% of patients experienced an adverse event that was considered to be related to treatment by the investigator.

A different ranking in the number or treatment related adverse events was observed between the paediatric and ≥ 12-year-old population. In the paediatric population, most drug related AE's were reported In the SOC Gastro intestinal disorders (18.2%), followed by the SOC Respiratory, Thoracic and Mediastinal disorders (16.7%), SOC Skin and subcutaneous tissue disorders (12.1%) and SOC investigations (10.6%).
For the population aged ≥ 12 years, most drug related AEs were observed in the SOC Respiratory, Thoracic and Mediastinal disorders (14.4%), followed by the SOC investigations (12.9%), the SOC Gastro intestinal disorders (10.9%), and Skin and subcutaneous tissue disorders (8.9 %).

This ranking of the SoC is on the one hand not unexpected, as the population aged ≥ 12 years suffers more from advanced pulmonary disease, while in the paediatric population gastro-intestinal symptoms might be more prominent. However, the data may also indicate that paediatric population might be more vulnerable to skin related adverse events.

Some new treatment-related adverse events were noted in the paediatric population. These adverse events were mostly of mild intensity and could also be considered as signs and symptoms of CF or other as symptoms of common disease manifestations (e.g., vomiting, cough, sputum increased, bronchospasm, haemoptysis, nasal congestion, pleuritic pain, rhinorrhoea, wheezing, bilirubin increased, aggression, anxiety, depressed mood, and fatigue).–Most of these events were reported as related or possible related to a single subject, mild to moderate in intensity and resolved upon ongoing use of ELX/TEZ/IVA. Therefore, they should not be mentioned in the ADR table of section 4.8 of the SmPC.

Cough (n=28) and sputum increased (n=3) were reported in more subjects in the paediatric population. However, these CF related adverse events were not reported with a higher frequency in the ≥12-year-old population compared with placebo. Therefore, the CHMP considered that they do not need to be included in the SmPC section 4.8.

Adverse events of special interest

In the adult and adolescent trials, identified adverse events of specific interest were transaminase elevation, rash and ocular lens opacity. These adverse events of interest also apply to the paediatric population.

Transaminase elevations
Transaminase elevations occur frequently in paediatric patients with CF and the inclusion of patients with transaminase elevation was limited to patients with ALT or AST < 3 × ULN. During the trial, the patients were regularly monitored. The reported incidence of transaminase elevation was (10.6%), in none of the patients did it lead to treatment discontinuation or treatment interruption.

The cross-study comparison with the safety data obtained in the patients aged ≥ 12 years showed a slightly higher incidence of transaminase elevation with the paediatric population (10.6 %) compared with the patients aged ≥ 12 years (7.9%). Unlike the patients aged ≥ 12 years, none of the paediatric population showed ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN (Table 35).

The cross-study comparison with the safety data obtained in the Symkevi trials (9.2%) and Orkambi trials (12.6%) revealed a comparable incidence of transaminase elevation (10.6%). However, these cross-study comparisons are hampered because of the more stringent the exclusion criteria in the

Kaftrio trials and of the longer observation period for Symkevi trials. In the VX-445/TEZ/IVA trials, patients were excluded when one out of the defined impairments were present instead of 2 (Symkevi) or 3 (Orkambi) trial, while the observation period for Symkevi was extended to 48 weeks. Therefore, the indirect cross study comparisons indicate that the risk of AESI-transaminase-elevated might be somewhat higher with Kaftrio compared to other CTFR modulators. Hepatoxicity is an important identified risk. Recently, the SmPC was amended to include a warning for frequent monitoring of ASAT/ALAT and bilirubin. At present, this risk appears to be sufficiently addressed, considering that the paediatric patients are treated in specialized clinics and will be frequently monitored.

Rash

Similarly to the adult and adolescent studies, treatment-related rash occurred frequently (n=8, 12.1% in part B).
It resulted in the discontinuation of treatment in one patient in part B of the study.

The cross-study comparison with the adult and adolescent data revealed that frequency of rash in the paediatric population was twice the frequency reported in the patients aged ≥ 12 years for both the AESI Rash-irrespective-of-causal-relationship (24.2 % vs 10.9 %), as well as the treatment-related Rash (12.1 % vs 6.9%). The current SmPC reports the AE-rash already as a very common adverse drug reaction (≥ 10%) in section 4.8. Therefore, no adjustment to the SmPC appears to be necessary.

Ocular lens opacity

None of the patients reported AEs related to ocular lens opacity. However, ocular lens opacities occur gradually and as such might be underreported. Therefore, patients must be examined before and after treatment. However, the study was conducted in the COVID-19 pandemic and not all patients underwent a post-treatment ophthalmic examination. Most patients (n=64) rolled over to the open label extension study 107, which also includes ophthalmic examinations. The results of this study will be awaited.

Incomplete safety measurements at end study due to COVID-19 pandemic

The study took place during the COVID pandemic, which might explain that no complete safety assessment including vital signs, ECG and ophthalmic examination was conducted in the complete safety population.

Data from 33 patients (50% of safety data set) were provided for the vital signs and ECG, while an unknown number of patients' results are provided for the additional ophthalmologic examination. The currently provided data do not raise concerns but are too limited to be conclusive. Nevertheless, the generated paediatric safety database can be supported with the generated safety profile obtained in patients aged ≥ 12 years, while additional long-term safety data will be provided (> 24 weeks) from the long-term roll over study 107.

2.7.2. Conclusions on clinical safety

ELX/TEZ/IVA is intended for chronic use. The provided paediatric safety data set is limited, both in patient numbers (n=66) and duration of treatment i.e., 24 weeks. In addition, the safety data is obtained in an uncontrolled, open-label, single-arm study in which the contribution from the longer disease duration versus the longer drug exposure is hard to distinguish.

The current safety data show that the treatment appears to be well tolerated in patients from 6 years of age, however it is noted that the AESI Rash occurred twice more often in younger children compared to the older population.

The transaminase elevation occurred with comparable incidence in the paediatric population as for older patients aged ≥ 12 years. It is an important identified risk and the SmPC contains sufficient recommendations for frequent monitoring.

In conclusion, the currently provided data set shows that the product is generally well tolerated, but the safety set is of limited duration (24 weeks) for a product intended for chronic use. Therefore, the additional long-term safety data obtained from study 107 should be provided once the data becomes available (by Q1 2023).

2.8. Risk Management Plan

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 6 to 11 years

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
Not applicable				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
Not applicable				
Category 3 – Required additional PV activities (by the competent authority)				
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
PASS Planned	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	Annual Reports	31 December 2021/2022/2023/2024
			Final Report	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 6 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 6 to 11 years	Final Report	February 2023

CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; F508del: an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein; MA: market authorisation; PASS: post-authorisation safety study; PD: pharmacodynamics; PV: pharmacovigilance; Q3: Quarter 3; Study 105: VX17-445-105; Study 107: VX19-445-107

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)
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)
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)

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)
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)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in children aged 6 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)

LFT: liver function test; PASS: Post-authorisation safety study; PL: Package Leaflet; PV: pharmacovigilance; Q3: Quarter 3; SmPC: Summary of Product Characteristics; Study 105: VX17-445-105; Study 107: VX19-445-107

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.0 is acceptable.

2.9. Pharmacovigilance

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.

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.

2.10. Product information

2.10.1. 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: limited changes introduced in this application.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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. The CFTR protein is an epithelial chloride channel responsible for aiding in 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. 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 the individuals in the US and 81.1% of the individuals in Europe)[6,7].

In this current variation, the following indication was initially claimed:

Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation (see section 5.1).

Available therapies and unmet medical need

In the treatment of CF, two main types of therapies can be distinguished, i.e., CF therapies that target the symptoms of the disease (such as nutritional supplements, antibiotics, and mucolytics), and CFTR modulators (i.e., correctors and potentiators) that maintain and improve lung function, reduce the risk of infections and exacerbations; and improve quality of life.

Correctors (such as tezacaftor and elexacaftor) facilitate the cellular processing and trafficking of mutant CFTR to increase the quantity of functional CFTR at the cell surface, resulting in enhanced chloride transport. CFTR potentiators (like ivacaftor) enhance the channel gating activity of the CFTR which is delivered to the cell surface (by correctors).

Kaftrio (elexacaftor/tezacaftor/ivacaftor, ELX/TEZ/IVA) is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene. Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) and Symkevi (tezacaftor/ivacaftor, TEZ/IVA) are CFTR modulators approved for CF patients with specific mutations.

The Kaftrio currently approved indication is for patients aged 12 years and older covers F/F genotypes, F/MF 'minimal function' genotypes, F/G 'gating' genotypes, and F/RF 'residual function' genotypes.

In children 6 through 11 years of age, approved modulator therapies are available for *F508del* homozygous patients (F/F), patients heterozygous for *F508del* and a specific residual function mutation (F/RF) or a specific gating mutation (F/G). Nevertheless, these treatments do not cure the disease and more efficacious treatments could fulfil this gap in these patients. For the populations heterozygous for

[6] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2019.
[7] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019

F508del and a minimal function mutation (F/MF) no treatment is available, which is an unmet need in this subpopulation.

3.1.2. Main clinical studies

To support an extension of the indication of ELX/TEZ/IVA to include CF patients 6 through 11 years of age with F/F or F/MF mutation, the efficacy and safety data of one clinical trial, study VX18-445-106 are submitted. The pharmacokinetics of ELX/TEZ/IVA is also investigated in study 106 that confirmed the dosing.

Study 106 is conducted in 2 parts (Parts A and B) to evaluate the pharmacokinetics, safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are heterozygous for *F508del* and a minimal function mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype).
Study 106 Part A evaluated ELX 100 mg once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h), which is half the dose that is approved for use in CF patients ≥12 years of age. Simulations were conducted to select a dosing regimen and the updated popPK models, which included PK data from adults, adolescents, and all Study 106 to confirm the proposed dosing regimen for Study 106 Part B.
Study 106-part B evaluated the safety and efficacy of ELX/TEZ/IVA in 24 weeks. The recommended total daily dose of ELX/TEZ/IVA for patients 6 through 11 years of age was evaluated, i.e.

- Patients weighing ≥30 kg: ELX 200 mg/TEZ 100 mg/IVA 300 mg
- Patients weighing <30 kg: ELX 100 mg/TEZ 50 mg/IVA 150 mg

The primary objective was safety; efficacy was secondary objective.

The secondary endpoints included spirometry and sweat chloride (SwCl), weight, height, body mass index (BMI) and associated z-scores, Cystic Fibrosis Questionnaire-Revised (CFQ-R), multiple-breath washout.

The extension of the indication to children 6 through 11 years old is based on the principle of partial extrapolation from adult 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 a medicinal product is to be used in younger paediatric patients for the same indication as those studied in older paediatric patients, the disease process is similar, and 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, the outcome of therapy is expected to be comparable in younger age groups compared to adults. Pharmacokinetic studies in the relevant age groups of paediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for paediatric use.

3.2. Favourable effects

Dosing

The results of Study 106 and popPK based simulations demonstrated that for subjects 6 through 11 years of age the distributions of individual ELX, TEZ, and IVA exposures, applying a dose of ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h dose in patients <30 kg and a dose of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in patients weighing ≥30 kg, were within the range of those observed in

subjects ≥18 years of age. Further, the M23-ELX exposures were within the clinical experience of ELX/TEZ/IVA, and M1-TEZ exposures were generally consistent with the expected clinical experience of ELX/TEZ/IVA and TEZ/IVA.

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

Efficacy

For the main secondary parameter ppFEV1, the LS mean absolute change in ppFEV1 from baseline through Week 24 was 10.2 percentage points (95% CI: 7.9, 12.6; p<0.0001). This is generally similar to the results in the adolescent and adult patients in the original marketing authorisation studies, when LS mean difference from baseline was 14.3 (95% CI 12.7, 15.8) in patients with F/MF mutations and 7.8%, (95% CI 4.8,10.8) for CFTR modulator experienced F/F patients and 13.2%, (95% CI (8.5,17.9) for CFTR modulator naïve F/F patients.

Treatment with ELX/TEZ/IVA resulted in the LS mean absolute change in SwCl from baseline through Week 24 of -60.9 mmol/L (95% CI: -63.7, -58.2; p<0.0001). These results are in line with results for the adolescent and adult patients in the original marketing authorisation studies (LS mean difference from baseline -42.2 mmol/L (95% CI: -44.0, -40.4) in patients with F/MF mutations and LS mean difference from baseline was -43.4 mmol/L (95% CI: -46.9, -40.0) and for patients with F/F mutations.

The within LS mean absolute change in CFQ-R Respiratory Domain Score of 7.0 points (95% CI: 4.7, 9.2; P<0.0001) was relevant, but less compared with results for the adolescent and adult patients in the original marketing authorisation studies (patients with F/MF mutations 20.2 points (95% CI 17.5,23.0) and patients with F/F mutations 17.4 points 95% CI 11.8,23.0)).

An improvement in ventilation inhomogeneity measured by LCI2.5 is shown by a numerical decrease from baseline. The LS mean absolute change in LCI2.5 from baseline through Week 24 was -1.71 (95% CI: -2.11, -1.30; P<0.0001). The natural variability for the LCI2.5 is 1 unit[8] or 15 % of baseline[9]. Therefore, the results are considered relevant.

Upon request from the CHMP, results at week 12 were also provided. The LS mean absolute change in ppFEV1 from baseline through week 12 was 9.6 percentage points (95% CI: 7.3, 11.9) and the LS mean absolute change in SwCl from baseline through Week 12 of -58.6 mmol/L (95% CI: -61.1, -56.1). The within LS mean absolute change in CFQ-R Respiratory Domain Score was 5.6 points (95% CI: 2.9, 8.2). The LS mean absolute change in LCI2.5 from baseline through Week 12 was -1.83 (95% CI: -2.18, -1.49).

3.3. Uncertainties and limitations about favourable effects

Because of the COVID-19 pandemic, many patients were unable to provide data on the efficacy endpoints toward the end of the study. Baseline data also appear to be missing for a small number of patients.
Despite the effort to collect as much efficacy data as possible, collection of data on the endpoints at week 16 and week 24 was hampered by the pandemic, and the option to provide efficacy data at an

[8] Singer F et al. Practicability of Nitrogen Multiple-Breath Washout Measurements in a Pediatric Cystic Fibrosis Outpatient Setting. Pediatric Pulmonology 2013; 48:739–746
[9] Oude Engberink et al. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. Eur Respir J 2017; 50: 1700433 https://doi.org/10.1183/13993003.00433-2017

unscheduled visit that was intended to supplement week 24 data may have introduced bias into the estimate of the outcome as these data may be from healthier, lower-risk patients.
Given the effect of a modulator on some parameters can already be observed around 4 to 8 weeks following treatment, additional analyses on the difference in the change through week 12 with all week 16 and week 24 data excluded from the analysis were conducted for all secondary endpoints. These analyses were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and demonstrate a robust and clinically meaningful improvements.
Based on the information provided on treatment discontinuation, the sensitivity analysis is essentially making the same (MAR) assumptions as the MMRM model. The lack of a control group limits the options for further sensitivity analysis.

3.4. Unfavourable effects

The safety profile is mainly determined by part B of the study, where 66 patients were treated for 24 weeks. The most frequently reported AEs (by PT are) were cough (n=28, 42.4%), headache (n=16, 24.2%) and pyrexia (n=14, 21.2 %).

Most frequently treatment related AEs were abdominal pain (n=6,9.1%), followed by alanine aminotransferase increase (n=5, 7.6%), rash (n=4, 6.1%) and headache (n= 4, 6.1%)

One patient prematurely discontinued treatment because of an adverse event i.e., rash erythematous. In two patients, treatment was temporality interrupted because of adverse events, i.e., 1 rash maculo-papular and 1 diarrhea, pyrexia, and vomiting.

Adverse events of specific interest were transaminase elevation and rash. A total of 7 (10.6%) paediatric patients experienced elevations of transaminases, and 16 (24.2%) experienced a rash.

3.5. Uncertainties and limitations about unfavourable effects

The main safety data set to support the application is of limited size in patient numbers (n=66) as well as in the duration of treatment i.e., 24 weeks. In addition, the safety data is obtained in an uncontrolled, open-label, single-arm study, in which the contribution from the longer disease duration is hard to distinguish from longer drug exposure.

Cross-study comparison showed the same frequency of transaminase elevation as with the other CFTR modulators Lumacaftor and Symkevi, although the exclusion criteria for patients with pre-existing liver function impairments were more stringent in ELX/TEZ/IVA studies compared to the Orkambi trials and Symkevi, and a prolonged observation period with the Symkevi trial.

The study was conducted during the COVID-19 pandemic, which resulted in an incomplete end of trial safety measurement. At the end of the trial, ECG and vital signs were conducted in 33 (50% of safety data set) subjects.

After completion of study 106, patients were invited to participate in the long-term safety study 107 of 96 weeks duration. A total of 64 patients rolled over. Additional long-term safety data will be provided once available (by Q1 2023).

3.6. Effects Table

Table 36 Effects Table for ELX/TEZ/IVA in the treatment of cystic fibrosis (CF) in patients aged 6 through 11 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.

Effect	Short Description	Unit	Treat-ment	Treatment in adults and adolescents (cross-reference) EMEA/H/C/005269/0000	Uncertainties/ Strength of evidence	References
Favourable effects						
ppFEV1	Change 0-24 wks. LS mean (95% CI) from baseline	%	10.2 (7.9, 12.6)	F/MF: 13.9 (12.8, 15.0) F/F: 10.4 (8.6, 12.2)	**SoE:** clinically relevant, magnitude in line with studies in adults and adolescents Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect. **Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison	Study 106 / EMEA/H/C/005269/0000
SwCl	Change 0-24 wks. LS mean (95% CI) from baseline	Mmol/l	-60.9 (-63.7, -58.2)	F/MF: -42.2 (-44.0, -40.4) F/F: -43.4 (-46.9, -40.0)	**SoE:** clinically relevant, magnitude in line with studies in adults and adolescents Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect. **Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison	
CFQ-R RD	Change 0-24 wks. LS mean (95% CI) from baseline	points	7.0 (4.7, 9.2)	F/MF: 17.5 (15.6, 19.5) F/F: 16.0 (12.1, 19.9)	**SoE:** clinically relevant, magnitude in line with studies in adults and adolescents Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect. **Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison	

Effect	Short Description	Unit	Treat-ment	Treatment in adults and adolescents (cross-reference) EMEA/H/C/005269/0000	Uncertainties/ Strength of evidence	References
BMI-z score	Change 0-24 wks. LS mean (95% CI) from baseline	Kg/ m^2	0.37 (0.26, 0. 48)	F/MF:0.34 (0.25, 0.44)	**SoE:** magnitude in line with studies in adults and adolescents **Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison	
Unfavourable effects						
Pex	Event rate/year		0.12	F/MF :0.37 F/F: 0.30	**Unc:** only a few events, open label, single arm study, indirect comparison	Study 106 / EMEA/H/C/005269 /0000
Abdominal pain		n, %	8 (12.1%)	9.9%	**Unc:** Limited safety data set (n=66) of limited duration (24 weeks) **Unc** data obtained in an open label study	
ALT increased	Alanine aminotransferase increased	n, %	7 (10.6%)	9.9%		
Rash (PT)		n, %	8 (12.1%)	8.9%		
Headache		n, %	16 (24.2%)	17.3%		
Bilirubin		N, %	1 (1.5%)	5.0%		

Abbreviations: CFQ-R = Cystic Fibrosis Questionnaire-Revised, Pex = pulmonary exacerbation(s), ppFEV1= percent predicted forced expiratory volume in 1 second, SwCl = sweat chloride.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of the favourable effects

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

The LS mean absolute change in ppFEV1 from baseline through Week 24 of 10.2% (95% CI: 7.9, 12.6;) is well above the accepted MCID in this population of approximately 2%. The results are considered clinically relevant.

The LS mean absolute change in SwCl from baseline through Week 24 of -60.9 mmol/l (95% CI: -63.7, -58.2) is also well above the accepted MCID of approximately 10 mmol/l. The results are considered clinically relevant.

Strength of the evidence

Pulmonary exacerbations and decline of lung function have an impact on survival in cystic fibrosis and reduce health-related quality of life. Preservation of lung function alongside reductions of the rate of pulmonary exacerbations are the main goals of the treatment of cystic fibrosis. ppFEV1 as a surrogate endpoint is a well-established endpoint and a reduction in the decline of FEV1 is related to improved survival. Observed improvements in ppFEV1 and SwCl were consistent with previous results in adults and adolescent populations. The results of ppFEV1 and SwCl are supported by all secondary parameters. CFQ-R respiratory domain, BMI z-score showed improvements well above the MCID. Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect.

Impact of the uncertainties

Not all known MF mutations can be tested in a clinical trial as in adult studies. The clinical benefit seen in the investigated F/MF patients has such a large effect size, that it was accepted that results of in the tested MF mutations can be extrapolated to all MF mutations. Moreover, additional studies in adults in F/G and F/RF mutations have established that ELX/TEZ/IVA is effective in all classes of mutations in the presence of at least one F508del mutation. Although not tested, in children a similar efficacy can be expected and extrapolation of efficacy is acceptable from paediatric patients with MF mutations to patients with at least one F508Del mutation.

Safety

In the adult clinical programs, ELX/TEZ/IVA appeared to be well-tolerated, both in the short term and in the long-term safety studies. The reported treatment-related adverse events in the paediatric population generally aligned with the reported events in patients aged ≥ 12 years.

Similarly to patients ≥ 12 years, the AESI rash occurred very frequently. In the paediatric population the AEsi Rash occurred twice as often compared with the patients aged ≥ 12 year, however no adjustment of the SmPC is needed, because rash is already reported as a very common adverse drug reaction.

The most frequent related AE is abdominal pain (6; 9.1%), followed by alanine aminotransferase increased (5; 7.6%).

In children, hepatic impairment and transaminase elevations appear to occur more slightly more frequently (10.6%) than in adults and adolescents (7.9%), but this is acceptable. The cross-study comparisons suggest a somewhat higher risk with Kaftrio for transaminase elevations than with other CFTR modulators, but head-to-head comparative data is missing. Like in adults and adolescents, the transaminases and bilirubin should be closely monitored, as already mentioned in the SmPC section 4.4.

After completion of study 106, patients were invited to participate in the long-term safety study 107 of 96 weeks duration. A total of 64 patients rolled over. So far, no study report for this trial has been submitted to provide extended safety data beyond 24 weeks of treatment.

3.7.2. Balance of benefits and risks

In this procedure, the extension of the indication to children 6 through 11 years old is based on the principle of partial extrapolation from adult and adolescents to paediatric patients. The extension needs to be supported by comparable PK exposures, and acceptable safety and a similar PD effect.

Indication

The currently investigated population of patients with F/MF genotypes or F/F genotype in study 106 is tighter than the population for which Kaftrio was recently granted a positive opinion for the older age group, i.e. patients 12 years and older with CF who have at least one *F508del*-mutation in the *CFTR*-gene.

Following approval of the above indication in parallel of this application and upon agreement from the CHMP, the requested indication was amended to *"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 further extrapolation to CF subjects 6 through 11 years of age with F/G and F/RF mutation is justified similarly that for CF patients with F/F and F/MF mutation. Additional evidence provided of the statistically significant benefits of ELX/TEZ/IVA over previously available CFTR modulators (IVA or TEZ/IVA) in CF subjects ≥ 12 years of age with F/RF and F/G genotypes was also provided.

Dosing

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

Efficacy

In this study in CF patients 6 through 11 years of age who are heterozygous for *F508del* and a minimal function mutation or homozygous for *F508del* mutation, efficacy was a secondary objective. The extrapolation is based on comparable exposure and safety.

Clinically relevant improvements were found in the changes from baseline for the ppFEV1 and SwCl. These improvements were consistent with previous results in adults and adolescent populations, confirming the justification of partial extrapolation.

Although many data were missing for the main statistical analysis, additional analyses on the change through week 12 with all week 16 and week 24 data excluded from the analysis were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and demonstrated a robust and clinically meaningful improvements.

Safety

The provided data showed that the treatment appears to be well tolerated in the paediatric population. The reported safety profile generally appears similar with the reported data obtained in the population aged ≥ 12 years. However, the safety data set was rather small (n=66), of limited duration (24 weeks) and is further hampered by missing data at the end of treatment safety follow-up due to the COVID-19 pandemic. The ongoing, extension study 107 will provide additional long-term safety and results will be provided upon completion (by Q1 2023).

Nevertheless, the safety profile of adult patients is well described, and the currently provided data did not identify new important risks. As expected, the paediatric population reported the highest frequency

of adverse events in the SoC Gastro-intestinal tract, while in the patients aged ≥ 12 years Respiratory events were more frequently reported.

Similarly to patients ≥ 12 years, the AESI rash occurred very frequently. The elevation of transaminases occurred slightly more frequently in the paediatric population compared to patients aged ≥ 12 years (10.6% vs 7.9%). Hepatotoxicity is already identified as an important potential risk. The earlier introduction of the modulator therapy in younger patients from 6 years of age might be beneficial, as this modulator therapy has the potential to prevent the long-standing detrimental effects of CF. Considering that these paediatric patients are treated in specialized clinics and frequently monitored, more uncertainties regarding the safety profile are considered acceptable and manageable in clinical practice. In addition, the safety will be further substantiated in the follow-up extension study 107.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Kaftrio is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP, by consensus, is of the opinion that Kaftrio is not similar to Kalydeco, Symkevi, Bronchitol, TOBI Podhaler within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

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 strength and the extension of the indication is favourable for the following indication:

Kaftrio is 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 (see section 5.1).

The CHMP did recommend the variation(s) to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension application to introduce a new strength of 37.5 mg/25 mg/50 mg Kaftrio film-coated tablets grouped with a type II variation (C.I.6.a) to include paediatric use (6 to 11 years) in patients with at least one F508Del mutation.

In addition, minor changes have been implemented in annex II according to the latest QRD template.

The RMP has been updated (version 5.0).
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 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.

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/0397/2020 and the results of these studies are reflected in the

Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Appendix

1. CHMP AR on similarity dated 11 November 2021.