27 February 2025
EMA/96436/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kaftrio	Ivacaftor / Tezacaftor / Elexacaftor
Kalydeco	Ivacaftor

Procedure No. EMEA/H/C/xxxx/WS/2551

Note

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

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List of abbreviations

Abbreviation	Term
AEs	Adverse events
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BLQ	below the limit of quantification
BMI	body mass index
CF	Cystic fibrosis
CFFT	Cystic Fibrosis Foundation Therapeutics
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RD	Cystic Fibrosis Questionnaire - Revised Respiratory Domain
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CFTR2-project	Clinical and Functional Translation of CFTR (CFTR2) project
CI	confidence interval
CK	creatine kinase
COVID-19	coronavirus disease-2019
CPAP	clinical pharmacology analysis plan
Ctrough	predose concentration
CV	coefficient of variation
DSMB	data safety monitoring board
ECG	electrocardiogram
ELX	Elexacaftor
ETT	Early Termination of Treatment
EU	European Union
ECFS	European Cystic Fibrosis Society
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDC	fixed-dose combination
FRT	Fischer Rat Thyroid
FSH	follicle-stimulating hormone
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPS	Global Patient Safety
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IV	intravenous
IVA	ivacaftor
IxRS	interactive response system in which X represents voice or web
LFT	liver function test
LS	least squares
LSM	least squares mean
M1-IVA	hydroxymethyl-ivacaftor, metabolite of ivacaftor
M1-TEZ	metabolite of tezacaftor
M23-ELX	metabolite of elexacaftor
max	maximum value
MF	minimal function
MI	multiple imputation
min	minimum value
MMRM	mixed-effects model for repeated measures
N	total sample size

n	size of subsample
N1	number of subjects with at least 1 non-missing measurement during the TE Period
OE	ophthalmological examination
P	probability
PD	pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbations
PK	pharmacokinetic
PN	Preferred Name
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
pwCF	people with CF
qd	once daily
q12h	every 12 hours
R117H	CFTR missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
RF	residual function
RNA	ribonucleic acid
SAE	serious AE
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	System Organ Class
SOP	standard operating procedure
SwCl	sweat chloride
TBILI	total bilirubin
TE	treatment-emergent
TEZ	tezacaftor
t-test	statistical test used when the independent variable is binary and the dependent variable is continuous
ULN	upper limit of normal
US	United States
USA	United States of America
y/o	years old
WHO	Drug World Health Organization Drug Dictionary

Glossary of Terms

Term	Definition
Study 124 (3-digit study number)	All clinical study numbers conducted with VX-445 (ELX, as monotherapy or combination therapy) are abbreviated to the last 3 digits (e.g., Study VX21-445-124 is Study 124).
Study 661-108 (6-digit study number)	Clinical studies conducted with other Vertex investigational drugs are abbreviated to the last 6 digits with the first 3 digits denoting the investigational drug and the last 3 digits denoting the study number (e.g., Study VX14-661-108 is Study 661-108)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Ireland) Limited submitted to the European Medicines Agency on 8 November 2023 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
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 and IIIB

Extension of the indication for Kaftrio (ivacaftor/tezacaftor/elexacaftor) and Kalydeco (ivacaftor) in a combination regimen to include the treatment of patients with cystic fibrosis (CF) aged 2 years and older who do not carry any F508del mutations and have at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene based on study VX21-445-124, study VX21-445-125 and study VX22-CFD-016.

As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the Kaftrio SmPC are updated; sections 4.1 and 5.1 of the Kalydeco SmPC are updated. The Package Leaflet is updated in accordance.

In addition, the worksharing applicant (WSA) took this opportunity to introduce editorial changes to the Product information.

The worksharing procedure requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Kaftrio, was designated as an orphan medicinal product EU/1/20/1468 on 21 August 2020. Kaftrio was designated as an orphan medicinal product in the following indication: Cystic fibrosis

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 Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0392/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP *P/0392/2023* 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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The WSA did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteurs for the WS procedure:

Peter Mol

Timetable	Actual dates
Submission date	8 November 2023
Start of procedure:	25 November 2023
CHMP Rapporteur Assessment Report	18 January 2024
PRAC Rapporteur Assessment Report	26 January 2024
PRAC Outcome	8 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 February 2024
Request for supplementary information (RSI)	22 February 2024
WSA's responses submitted to the CHMP on:	27 March 2024
CHMP Rapporteur Assessment Report	01 May 2024
PRAC Rapporteur Assessment Report	03 May 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	16 May 2024
CHMP members comments	17 May 2024
Updated CHMP Rapporteur Assessment Report	24 May 2024
2nd Request for supplementary information (RSI)	30 May 2024
List of Questions to AHEG	30 May 2024
WSA's responses submitted to the CHMP on:	23 July 2024
CHMP Rapporteur Assessment Report	26 August 2024
CHMP members comments	06 September 2024
Updated CHMP Rapporteur Assessment Report	18 September 2024

Timetable	Actual dates
3rd Request for supplementary information (RSI)	19 September 2024
AHEG	28 November 2024
WSA's responses submitted to the CHMP on:	20 December 2024
CHMP Rapporteur Assessment Report	05 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur Assessment Report	21 February 2025
CHMP Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

With the current worksharing application, an extension of the indication is pursued for Kaftrio (ivacaftor/tezacaftor/elexacaftor) and Kalydeco (ivacaftor) in a combination regimen, to include the treatment of patients with cystic fibrosis (CF) aged 2 years and older who do not carry any *F508del* mutations and have at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Disease or condition

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 in these organs results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the CFTR protein can result 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.

All people with CF (pwCF) have a CFTR mutation in both copies of the CFTR gene. The severity of CF is determined by the extent of the loss of CFTR-mediated chloride transport caused by the 2 CFTR mutant alleles that result in dysfunction of the CFTR-mediated chloride transport
Severe CF is characterized by a complete or near complete loss of the CFTR function. It is characterised by early onset and relatively rapid disease progression, with sweat chloride (SwCl) concentrations typically greater than 90 mmol/L.
In contrast, those mutations that cause a more modest reduction in CFTR-mediated chloride transport (e.g., residual function mutations) result in slower symptom progression and lower SwCl concentrations;

however, people with CF and these mutations still develop severe disease characterized by chronic pulmonary disease, PEx, and premature death.

State the claimed therapeutic indication

With the current application, the WSA proposes to extend the proposed indication for a total of 183 non-F508del mutations claimed to be responsive to ELX/TEZ/IVA based on in vitro and/or clinical data. The current indication is restricted to CF patients harbouring at least one F508 del mutation. With the proposed extension of the indication, also patients not harbouring a F508del mutation may have access to Kaftrio.
This submission initially proposed to extend the indication of Kaftrio (elexacaftor/tezacaftor/ivacaftor) and Kalydeco (ivacaftor) as follows:

Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene **or a mutation in the CFTR gene that is responsive based on clinical and/or *in vitro* data** (see section 5.1).

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

Kalydeco tablets are indicated:
[…]

In a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who have at least one *F508del* mutation in the *CFTR* gene **or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data** (see section 5.1).

…

Kalydeco granules are indicated:
[…]

In a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one *F508del* mutation in the *CFTR* gene **or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data** (see section 5.1).

Epidemiology

CF affects approximately 54,000 in Europe (including Russia, Turkey and Israel) and 32,000 individuals in the United States.[1,2] The incidence and prevalence of CF varies between racial groups; CF is considerably more common in the Caucasian populations of Europe and North America than in Asian and African populations.

Based on the 2021 report from the European CF Society Patient Registry (ECFSPR) that included data on 54,043 patients with CF from 40 countries in the EU,[3] 80.3% of the patients with available genotype data and who were seen in 2021 had at least one *F508del* allele. Of the 54,043 CF patients, the median age was 19.8 years and of the total population 54% were older than 18 years of age.

[1] European Cystic Fibrosis Society. 2021 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2023.
[2] Cystic Fibrosis Foundation Patient Registry. 2021 annual data report. Bethesda, MD: Cystic Fibrosis Foundation; 2022.

People with CF who do not carry at least one *F508del* mutation are rare (~20% of CF population) and have CFTR mutations that are individually rare. This submission focuses on a subset of 183 non-*F508del* mutations that have been identified as responsive to elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor based on clinical study, noninterventional real-world evidence (RWE), and/or in vitro data. ECFSPR data show that these 183 mutations are found in approximately 40% of the Europeans with CF who have no *F508del* CFTR mutation (data on file requested by Applicant). The current extension of the indication will affect about 8% of the total CF population.

Aetiology and pathogenesis

CF is a life-shortening, autosomal recessive disease caused by mutations in the CFTR gene. All people with CF have a mutation in both copies of the CFTR gene. More than 2,000 CFTR gene mutations have been identified[3]. Not all CFTR mutations are CF-causing. The most frequently reported CF-causing mutation is the *F508del* mutation and the vast majority of people with CF carrying either 1 or 2 copies of the *F508del*-CFTR mutation.

The CFTR protein is an epithelial chloride ion 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.

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

- Class I mutations: Defective protein production
- Class II mutations: Defective protein processing
- Class III mutations: Defective regulation
- Class IV mutations: Defective chloride conduction
- Class V mutations: Reduced amounts of functional CFTR protein (less transcription)

Alternative classification

CF-causing mutations can be divided into two 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 (MF) of CFTR (class I, II and III). A less complete loss of CFTR-mediated chloride transport is referred to as "residual function" (RF) of CFTR (class IV and V). The MF/MF genotype is usually associated with severe CF disease with sign and symptoms presenting at early age. Patients with MF/RF or RF/RF genotype may have milder forms of disease, with some presenting with symptoms later in life, but with a reduced life expectancy compared with a non-CF population.

Clinical presentation, diagnosis

In Europe the median age of all CF patients was 19.8 years (with youngest patient being diagnosed just after birth and the oldest patient being 87.4 years of age) in 2021.[3] Despite advances in treatment, the current median age of death in a patient with CF is 33 years. Respiratory disease remains the predominant cause of death (46.8% of all deaths in 2021).

In the early days, CFTR genotyping was done in individuals with clear phenotypic manifestations of CF and who demonstrated CFTR dysfunction through sweat chloride measurement. Therefore, if a mutation was detected in the CFTR gene in a sample from an individual with CF, it was presumed to be CF-causing. However, with improved genotyping techniques, it became clear that not all CFTR mutations are

[3] Cystic Fibrosis Mutation Database (CFTR1). http://www.genet.sickkids.on.ca/StatisticsPage.html..

associated with CFTR dysfunction or CF.

Usually, the diagnosis of CF is straightforward, with two identified CF causing CFTR mutations while the patient has a baseline SwCl ≥ 60 mmol/L. However, the diagnosis will become more complicated if the baseline SwCl is < 60 mmol/L or if at least one CFTR mutation is found that is non-CF causing or if the clinical relevance of the CFTR mutation is not known. In these cases, additional CFTR function testing (nasal potential difference (NPD), intestinal current measurement (ICM) is done to confirm (or exclude) the diagnosis of CF. However, if these tests are inconclusive or not available, a careful clinical work up (preferably by a CF centre) is needed to confirm the diagnosis of CF.

With the more frequently occurring genetic analyses, CFTR mutation variants were identified, that were not independently causal of CF. To address the need for the annotation of CFTR variants, the US CF Foundation assembled an international research group tasked with defining criteria for disease liability and annotating the mutations seen in patients with CF. i.e. the clinical and functional translation of CFTR project (CFTR2 project).

The CFTR2 project has assembled data from national registries of patients with CF, as well as large clinical databases from countries without a national registry, to collect, quantify, and describe the CFTR mutations reported in individuals with CF. The data is obtained from Europe, North America, Australia, but also contain representation from the Middle East, Asia and South America.

A CFTR2 committee determines if a CFTR mutation will be CF causing, of varying clinical consequence or non-CF causing.

The CFTR2 uses clinical criteria, functional analyses and population penetrance to categorise the CFTR mutations4. In short,

- For CFTR mutations classified as CF causing, these CFTR mutations will cause CF, if the mutation is present in trans with a known CF-causing mutation.
- For CFTR mutation of "varying clinical consequences", there might be a lack of CF phenotype if this particular mutation occurs in trans with a known CF-causing mutation, while other patients clearly suffer from CF.
- For those CFTR mutations that are classified as "non-CF causing", the committee has sufficient evidence that the CFTR mutation does not cause CF based on the clinical presentation, function and population penetrance obtained from the provided data.

The CFTR2 team consists of leading scientists from Johns Hopkins University in Baltimore, MD, the Hospital for Sick Children in Toronto, Canada, and the Cystic Fibrosis Centre in Verona, Italy. This research group, has made an important contribution to better informed genetic analysis as a part of CF diagnosis.[5]

The European Cystic Fibrosis Society (ECSF) refers to this CFTR2 project when genetics are used to diagnose a patient with CF.

The complete CF diagnosis criteria by the ECFS are:

- the presence of a positive NBS test result **or**
- clinical features suggestive of CF, including, but not restricted to, diffuse bronchiectasis; positive sputum cultures for a CF-associated pathogen (e.g. Pseudomonas aeruginosa); exocrine pancreatic insufficiency; salt loss syndrome,
- and obstructive azoospermia in males

[4] Sosnay PR, Salinas DB, Whithe TB et al. Applying cystic fibrosis transmembrane conductance regulator genetics and CFTr2 data to facilitate diagnoses. J Pediatr 2017; 181S: S27-32.
[5] Sosnay PR, Salinas DB, Whithe TB et al. Applying cystic fibrosis transmembrane conductance regulator genetics and CFTr2 data to facilitate diagnoses. J Pediatr 2017; 181S: S27-32.

- and a sweat chloride > 59 mmol/L and/or two CF-causing CFTR mutations in trans6 .

CF may have overlap with many other respiratory diseases, but a clear diagnosis of CF is essential. A diagnosis of CF may give immediate access to specialised CF care; however, a diagnosis of CF might also have important psychological and social implications. Therefore, a patient should be carefully evaluated before the diagnosis of CF is made.

Management

Existing treatments for CF can be broadly classified into two 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) that target the underlying cause of the disease. Concomitant administration of these two groups is recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life. However, not all CFTR genotypes are indicated for approved modulator therapies, and not all patients are able to tolerate the therapy.

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 authorised 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 facilitate the cellular processing and trafficking of CFTR to increase the quantity of CFTR at the cell surface. Potentiators 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 results in sufficient levels of CFTR at the surface, which is then enhanced for its gating function.

2.1.2. About the products

Kaftrio and Kalydeco belong to the pharmacotherapeutic group of other respiratory system products with Anatomic Therapeutic Chemical (ATC) code R07AX31.

Kaftrio is a triple combination product which contains the CFTR modulators elexacaftor (ELX), tezacaftor (TEZ) and ivacaftor (IVA).

ELX is a CFTR corrector that facilitates the cellular processing and trafficking of multiple mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of functional CFTR protein delivered to the correct location in the cell surface, resulting in increased chloride transport. TEZ, also a CFTR corrector, in combination with ELX is additive to the effect of ELX alone. IVA is a CFTR potentiator that increases the channel open probability (or gating) of CFTR at the cell surface to enhance chloride transport. For IVA to function, CFTR protein must be present at the cell surface. IVA can potentiate the CFTR protein delivered to the cell surface by ELX and TEZ, leading to a further enhancement of chloride transport than achieved with single or dual therapy alone.

In the EU, Kaftrio is approved in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

[6] Castellani et al. ECFS best practice guidelines: the 2018 revision. J of Cystic Fibrosis 2018(17:153-178.

The F508-Del population accounts for about 80% of the population with CF, i.e., a disease with an orphan designation. The complementary non-F508del population accounts for about 20% of the CF population and includes about 8500 EU CF patients.

A specific subgroup among the non-F pwCF is the pwCF homozygous for class I CFTR variants. The class I CFTR variant does not produce protein, while modulator therapy needs this protein for binding to be effective. Class I mutations are e.g. nonsense mutations, in-frame deletions. The homozygous class I CF population covers 3 to 5% of the overall CF population.

The complementary non-F508del population covers 15 to 17% of the CF population. The rarity of the non-F pwCF makes it hard to conduct a clinical trial in this population. Moreover, this non-F population harbours a large number of CFTR variants (> 2000). There are regional differences in the prevalence of non-F CFTR variants. The non-F mutations are individually rare, particularly when in trans with another non-F CFTR variant.

These CFTR variants may also contribute to different phenotypes. Some of these variants are clearly CF-causing, while others may have varying clinical consequences or their clinical relevance cannot be determined due to the ultra-rarity of the mutation, particularly when not occurring with the F mutation in trans.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice

No scientific advice was requested.

2.2. Non-clinical aspects

2.2.1. Introduction

The clinical package provides the results of a placebo-controlled trial in the non-pwCF population. Such a trial was considered possible because Kaftrio is the first modulator applied for this population, the CF community is well organised and pwCF are generally treated in specialised CF centres.

This RCT data is additionally supported with Real World Data obtained from 2 registry based, observational studies. The first study used data from a US registry limited to CFTR mutations that showed a positive response in the Fischer Rat Thyroid in-vitro assay. The second study used data obtained from the expanded French Compassionate Use program, which only excluded pwCF with two variants previously characterised as not responsive.

Fischer Rat Thyroid (FRT) cells are used as a model system allowing for more systematic assessment of the effects of CFTR modulator(s) on CFTR-mediated Cl^- transport to identify *CFTR* mutations that are responsive in vitro. One allele of the CFTR (mutant) cDNA is inserted in the genomic DNA of the FRT cell line.

In this in vitro model, the function of CFTR at the cell surface is directly assessed in Ussing chamber studies. The Ussing chamber studies quantify the amount of CFTR-mediated Cl^- transport ($\mu A/cm^2$) in FRT cells expressing each mutant *CFTR* form as a fraction of the Cl^- transport in FRT cells expressing normal CFTR (% normal). A positive response is defined as a 10-pp increase in *in vitro* Cl^- transport over baseline when expressed as a percentage of normal CFTR Cl^- transport.

In addition to measuring functional response, the improvement in the processing and trafficking of mutant CFTR protein was assessed in Western blot studies that measured both the amount of mature and immature CFTR protein.

The FRT assay did not go through an EU qualification procedure and therefore, it is not a priori considered a qualified test to support an application.

2.2.2. Pharmacology

Study P289 has been performed to assess pharmacological response to the FRT assay.

Objective

The objective of this study was to systematically characterize the pharmacological response of 235 CFTR mutations to different CFTR modulator therapies (the triple combination of ELX/TEZ/IVA, the dual combination of TEZ/IVA and the monotherapy IVA) in a panel of Fischer rat thyroid (FRT) cells each expressing one rare CF-causing mutation in order to support the approval for patients where clinical trials are challenging. A prespecified threshold was applied of 10-percentage point (pp) increase in in vitro chloride transport over baseline when expressed as a percentage of normal CFTR chloride transport. This threshold was previously used in the FDA submissions for IVA and TEZ/IVA as a threshold for likely clinical benefit. The 10% threshold is both (a) aligned with natural history studies suggesting that 10% of normal CFTR function is associated with less severe disease progression, and (b) has been shown to be predictive of clinical response in multiple clinical studies.

CFTR Mutations Selected for Testing

A non-exhaustive set of 235 CF-causing mutations was selected for study based upon the following 2 criteria:

1. Evidence that the mutation is CF-causing as listed in the CFTR2 (www.CFTR2.org) database and/or in the scientific literature, and

2. In silico translation consistent with production of full-length CFTR protein (e.g. missense mutations or small insertion and/or deletion mutations that are in-frame).

FRT cells were engineered each to express one of the rare mutations, and the following control FRT cells lines were included as comparators for the Western blot and Ussing chamber studies:

- Un-transfected (parental) FRT cells: used to establish baseline and noise threshold for the system
- Wild-type (normal)-CFTR: used to normalize chloride transport to normal (% normal)
- F508del-CFTR: the most common CF-causing mutation and subject of FDA approvals for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA therapies
- Positive controls: two CFTR mutations (*G551D* and *R117H*) that were responsive in previous FRT studies and have been demonstrated in clinical trials to be IVA-responsive (Studies 770- 102, 770-103, and 770-110)
- Negative controls: three CFTR mutations (*G1061R*, *R1066C* and *N1303K*) that were not responsive to IVA or TEZ/IVA in previous *in vitro* studies

Excluded from this study are mutations in CFTR that truncate the protein and/or delete all or partial CFTR gene sequences, as these mutations do not produce full-length CFTR protein. Additionally, splice

mutations are not included because the FRT system uses a cDNA that is correctly spliced, and thus are not suitable for testing in this system.

Materials

CFTR Modulator Concentrations for Evaluation

Vehicle (DMSO) and three CFTR modulator mono- or combination therapies were evaluated (IVA, TEZ/IVA, and ELX/TEZ/IVA) in the presence of serum in order to better mimic in vivo conditions and to most closely match the protein unbound clinical exposures. The concentrations of IVA and TEZ were fixed at 1 and 10 µM, respectively, to be consistent with a clinically relevant exposure range and to be consistent with concentrations used previously to evaluate TEZ/IVA. For ELX, a 6-point dose response consisting of 0, 0.1, 0.3, 1, 3, and 10 µM of ELX was tested. The data generated with 10 µM ELX was used to determine TC-responsiveness.

Methods

Cell Line Generation and Culture

FRT cell lines expressing mutant CFTR mutations were generated using a standardized protocol derived from the protocol previously reported. FRT cell lines were characterized at the time of Western blot and Ussing chamber studies for gene expression level by semi-quantitative RTPCR to ensure that the expression level is within 2-fold of the FRT cell line expressing normal CFTR. Gene sequencing was performed to confirm that the appropriate mutation is present. If a cell line failed to meet one or both of these criteria, cells from an additional cryovial of the original cell culture were evaluated. If the cell line failed to meet the criteria a second time, the cell line was excluded from the study.

Western Blot Analysis

To monitor CFTR maturation in Flp-InTM-FRT cells stably expressing CFTR mutations, cells were incubated with DMSO, 1 µM IVA alone, 10 µM TEZ/1 µM IVA or 10 µM ELX/10 µM TEZ/1 µM IVA in 200 µL/well complete FRT cell culture medium for 18 – 24 hours at 37 °C to allow for the de novo synthesis, processing, and trafficking of CFTR protein to reach steady-state levels. Serum (10% fetal bovine) was included during the incubation in order to better mimic in vivo conditions. Cells were lysed and prepared for western blotting.

To quantify CFTR maturation, bands for immature and mature CFTR were normalized to an internal loading control protein (GAPDH). Lysate from normal CFTR (FRT wild-type CFTR clone B) was included on every gel to calculate percent normal CFTR. Values were determined from 4 independent experiments using a well-validated CFTR antibody. Periodically throughout the course of the study the parental, normal (wild-type-) CFTR, and *F508del* FRT cell lines were evaluated by Western blot to ensure consistent assay performance across time and operators. Data generated for QC purposes was not included in the test set.

Using Chamber Recordings

Ussing chamber studies were performed to determine (1) the baseline level of CFTR-mediated chloride transport for each mutant cell line and (2) if CFTR modulators increase the CFTR-mediated chloride transport. Ussing chamber studies were performed as described in the standardized protocol. As in Western blot studies all compounds were added in the presence of serum for 18 – 24 hours prior to testing. Chloride transport was stimulated by addition of forskolin (10 µM) and then subsequently inhibited by a cocktail of CFTR inhibitors. The short circuit current (e.g. current attributable to CFTR) was calculated as the peak Forskolin (FSK)- stimulated response minus the minimum stable chloride current after addition of the CFTR inhibitor cocktail. The minimal detectable chloride current in Flp-InTM-FRT without an introduced CFTR gene is 4 ± 1 µA/cm2, and this value was considered equivalent to that of cells lacking CFTR-mediated chloride transport. The current induced by wild type CFTR was also

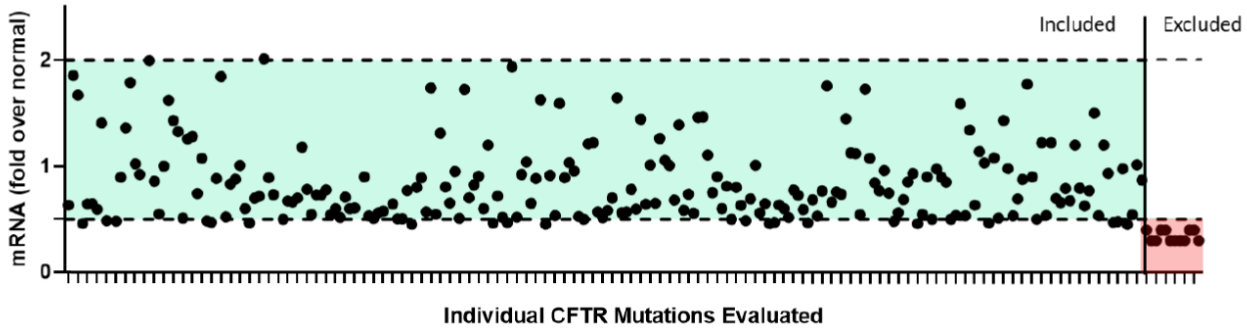
measured. For each mutation, chloride transport is reported as µA/cm2 and also as a percent of wild type CFTR (% normal). Percent normal was calculated by dividing the µA/cm2 value of the CFTR mutant form by the µA/cm2 value of baseline normal CFTR. The baseline normal CFTR value was determined from the first six valid experiments and used for all calculations throughout the duration of the study. Each valid, independent experiment consists of: 1) cell plating on a day that is different from other experiments with the same cell line, 2) Ussing chamber studies performed on a day that is different from other experiments with the same cell line, and 3) one or two technical replicates per condition studied. The net difference in chloride transport attributable to the CFTR modulator(s) was determined by subtracting the % normal value for baseline for a given FRT cell line from the % normal of the compound treated value for the same FRT cell line. Values were determined for each CFTR mutation from six valid, independent experiments. Periodically throughout the study, the parental FRT line, normal (wildtype)- CFTR, and *F508del*-CFTR were evaluated to ensure that the assay was performing consistently across time and operators. Data generated for QC purposes was not included in the test set. In addition, instrument QC was performed periodically to ensure consistent function of the Ussing chamber equipment.

Results; Generation and Characterization of a Panel of FRT Cell Lines

Expressing Mutant Mutations of CFTR

A panel of stable cell lines was generated using FRT cells to allow for the systematic comparison across multiple mutant CFTR forms of the pharmacological activity of ELX/TEZ/IVA, TEZ/IVA, and IVA. Each cell line in the panel was engineered to express a single mutant CFTR form observed in people with CF (in some cases this involves multiple changes as compared to wild type, i.e., complex alleles). Gene expression levels were measured by semi-quantitative RTPCR to ensure that the expression level is within 2-fold of the FRT cell line expressing normal CFTR and gene sequencing was performed to ensure that the appropriate mutation is present. Of the 235 CFTR mutations selected for testing, 219 cell lines (plus F508del) had the correct sequence and met the inclusion criteria for CFTR expression. Specifically, the level of CFTR mRNA expression for the 219 cell lines were within 2-fold (0.5 – 2.0) of the FRT cell line expressing normal CFTR, suggesting that the level of CFTR mRNA expression was generally similar between normal CFTR and the panel of mutant CFTR forms (**Figure *1***). The remaining cell lines were excluded from the study due to either low mRNA levels (12 cell lines; see the red box at the bottom right of **Figure *1***) or displaying the incorrect sequence (3 cell lines; not shown in **Figure *1***).

Figure 1: CFTR mRNA Expression in Panel of FRT Cells Legend: CFTR mRNA expression in FRT cells. Mean levels of CFTR mRNA expression for each mutant CFTR form expressed in FRT cell containing the Flp Recombination Target site (pFRT/lacZeo). For each mutant CFTR form, the level of CFTR mRNA expression was normalized to the level of normal CFTR expression in a single FRT cell line. For inclusion in the study, the level of CFTR mRNA expression must be within 2-fold (0.5 – 2.0; green shaded area) of the FRT cell line expressing normal CFTR. Cell lines for which the mRNA levels were outside this range were excluded for the study (red shaded area).



Effect of ELX/TEZ/IVA, TEZ/IVA and IVA on CFTR Processing

The delivery of mutant CFTR protein to the cell surface was assessed in Western blot studies that measure the amount of mature and immature CFTR protein. In the absence of CFTR modulators, there was a range in the amount of mature CFTR protein when expressed as either the ratio of mature CFTR protein to total CFTR protein (mature / mature + immature) or as a % of normal CFTR protein (Table 2). This is expected, as different mutant CFTR forms are known to cause a range in the severity of the defect in CFTR processing, resulting in a range in the amount of CFTR protein delivered to the cell surface.

As expected, based on the well-characterized mechanism of action, treatment with IVA alone had little-to-no effect on the processing of mutant CFTR. In contrast, treatment with ELX/TEZ/IVA improved CFTR processing when compared to vehicle for both *F508del*-CFTR and for the majority (n=194) of other mutant CFTR forms tested. For 80 mutations (including *F508del*-CFTR) the improvement due to ELX/TEZ/IVA in CFTR processing was greater than that achieved with TEZ/IVA. For some mutant CFTR forms (n=138), the improvement in CFTR processing was similar between ELX/TEZ/IVA and TEZ/IVA. For these mutant CFTR forms, TEZ/IVA typically resulted in normal CFTR processing that was not further improved by ELX/TEZ/IVA. A minority (n=15) of mutant CFTR forms had severe defects in CFTR processing that were not improved by either TEZ/IVA or ELX/TEZ/IVA.

Effect of ELX/TEZ/IVA, TEZ/IVA and IVA on CFTR Function

The function of CFTR at the cell surface was directly assessed in Ussing chamber studies. The Ussing chamber studies quantify the amount of CFTR-mediated chloride transport (μA/cm2) in FRT cells expressing each mutant CFTR form as a fraction of the chloride transport in FRT cells expressing normal CFTR (% normal). Chloride transport in FRT cells that do not express CFTR was ~1% of normal CFTR (Table 3), showing the response to be specific to CFTR protein. A positive response to a CFTR modulator regimen was defined as a statistically significant, ≥10 percentage point increase over baseline in chloride transport, expressed as a percentage of normal CFTR function.

As expected, in the absence of CFTR modulators the baseline activity of CFTR-mediated chloride transport varied across the different mutations. This is due to differences among the mutant CFTR forms in the severity of the defects in CFTR processing, channel gating activity (channel open probability), and/or conductance (rate of ion transport).

Consistent with clinical data, ELX/TEZ/IVA increased chloride transport in FRT cells expressing *F508del*-CFTR to a level that was ≥10% of normal over baseline (i.e. responsive) while the increase observed with TEZ/IVA was below 10% of normal (i.e. not responsive). While IVA has little effect on *F508del*-CFTR in the absence of a corrector, IVA alone did increase chloride transport as expected in *G551D*-CFTR and *R117H*-CFTR. Finally, as expected, the negative controls (*G1061R*, *R1066C*, and *N1303K*) were not responsive to IVA and TEZ/IVA/ELX.

In addition to *F508del*-CFTR, 80% of the mutant CFTR forms accepted in the study (175 of 219 mutations) were responsive to ELX/TEZ/IVA (**Table *1***). These included mutations in the Symkevi or Kalydeco USPI and previously un-characterized CFTR mutations. Within the ELX/TEZ/IVA-responsive mutation group, a total of 127 mutations not currently in the Symkevi USPI were identified to be TEZ/IVA-responsive (117 newly characterized mutations and 10 previously characterized gating mutations) and a total of 59 mutations not currently in the Kalydeco USPI were identified as IVA-responsive. Forty-three mutations were not responsive to any of the CFTR modulator regimens tested using the threshold of 10% of normal CFTR function.

The broader spectrum of activity for ELX/TEZ/IVA when compared to TEZ/IVA or IVA is due to the ability of triple combination therapy to result in high levels of functional CFTR at the cell surface. Kaftrio is comprised of two CFTR correctors, ELX and TEZ, that act through distinct mechanisms of action to improve CFTR processing, and a CFTR potentiator, IVA, which increases the channel gating of the CFTR delivered to the cell surface.

Table 1: Overview of Newly Characterized Mutations Responsive to ELX/TEZ/IVA, TEZ/IVA, and/or IVA

CFTR modulator regimen	**Current EU indication**	**Characterised responsive mutations (previously + new)**
Kaftrio/Kalydeco Proposed MAH indication 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 or a~~ one mutation in the Cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive based on clinical and/or in vitro data (see section 5.1).	F/any Proposed indication F/Any Harbouring at least a E/T/I responsive CFTR mutation.	175+337
TEZ/IVA (Symkevi) Approved indication Symkevi is indicated in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T	F/F + F/one of the following mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T	26+117
Ivacaftor (Kalydeco) (as monotherapy) Approved indication As monotherapy for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an R117H CFTR mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).	CF patients harbouring R117H or one of these specific gating mutations *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*	38+59

Approved indication Kalydeco is indicated for the treatment of infants aged at least 1 month, toddlers and children weighing 3 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R* (see sections 4.4 and 5.1)		

Consistent with the known mechanism of action for CFTR potentiators, those mutations that are IVA-responsive typically had evidence of CFTR at the cell surface.

In vitro studies using HBE cells derived from patients with one or two copies of F508del-CFTR along with supportive clinical data have demonstrated that the triple combination provides a greater increase in chloride transport when compared to TEZ/IVA or IVA. Consistent with these findings in HBE cells, ELX/TEZ/IVA improved CFTR processing and function more than TEZ/IVA or IVA in FRT cells expressing *F508del*-CFTR and multiple other mutant CFTR forms. For some mutant CFTR forms, the improvement in CFTR processing and chloride transport was similar between ELX/TEZ/IVA and TEZ/IVA. For these specific mutant CFTR forms, treatment with TEZ/IVA typically resulted in normal CFTR processing that was not further improved by ELX/TEZ/IVA, suggesting that a maximal amount of mutant CFTR protein was delivered to the cell surface.

Among the more than 2,000 CFTR variants identified to date at least one (the *G970R* variant) has been shown to encode a cryptic exonic splice defect that results in reduced full-length CFTR protein in naïve tissues derived for CF patients. Whereas the full length *G970R*-CFTR protein was responsive to ivacaftor when expressed in FRT cells using cDNA, the cryptic exonic splice variant observed in patient-derived cells is not responsive to ivacaftor. To identify other potential cryptic exonic splice CFTR variants, 1,432 unannotated CFTR variants were evaluated *in silico* (Lee et al., 2017). Of these, 2% (n = 32) were bioinformatically nominated as potentially encoding a cryptic exonic splice site. In the current study of FRT cells, 7 of these CFTR variants (*M152V, I175V, W361R, E403D, S589N, G970D*, and *H939R*) were responsive to one or more CFTR modulators and bioinformatically nominated as encoding a potential cryptic exonic splice variant. All of these 7 CFTR variants are individually exceptionally rare with the most common being *G970D* (n = 10 people in the CFTR2.org database). Despite the bioinformatic prediction of potential for a cryptic exonic splice site, laboratory studies show that the *G970D* variant in fact produces a full-length CFTR protein that is responsive to CFTR modulators in patient-derived cells. The example of *G970D* highlights that whereas *in silico* tools can be useful to nominate potential cryptic exonic splice variants, they also have the potential to misclassify CFTR variants that encode a full-length CFTR protein. Based on the laboratory data showing responsiveness in FRT cells, as well as the uncertainty of *in silico* predictions of cryptic exonic splicing, 6 potential cryptic exonic splice variants were included in the study (*M152V, I175V, W361R, E403D, S589N*, and *H939R*) but annotated as having bioinformatic annotations as possibly encoding a cryptic exonic splice site.

Table 2: CFTR mutations identified to be responsive based on clinical and/or in vitro data (reference to section 5.1 of SmPC)

1140-1151dup	E264V	I105N	P5L[†]	S557F

1336K	E282D	I1139V	P67L*	S589I
1461insGAT	E292K	I1203V	P750L	S589N
1507_1515del9	E384K	I1234L	P798S	S624R
2055del9	E403D	I1234V	P988R	S686Y
2183A→G	E474K	I1234V	Q1012P	S737F
2789+5G→A*	E527G	I125T	Q1209P	S821G
2851A/G	E56K	I1269N	Q1291H	S898R
293A→G	E588V	I1366N	Q1291R	S912L
3007del6	E60K	I1366T	Q1313K	S912L;G1244V‡
3132T→G	E822K	I148L	Q1352H	S912T
3141del9	E831X	I148N	Q151K	S945L*†
3143del9	E92K	I175V	Q179K	S955P
314del9	F1016S	I331N	Q237E	S977F
3272-26A→G*†	F1052V	I336L	Q237H	S977F;R1438W‡
3331del6	F1074L	I444S	Q237P	T1036N*
3410T→C	F1078S	I497S	Q30P	T1057R
3523A→G	F1099L	I502T	Q359K;T360K‡	T1086A
3601A→C	F1107L	I506L	Q359R	T1086I
3761T→G	F191V	I506V	Q372H	T1246I
3791C/T	F200I	I506V;D1168G‡	Q493L	T1299I
3849+10kbC→T*†	F311del	I521S	Q493R	T1299K
3850G→A	F311L	I530N	Q552P	T338I
3978G→C	F312del	I556V	Q98P	T351I
546insCTA	F433L	I586V	Q98R	T351S
548insTAC	F508C;S1251 N‡	I601F	R1048G	T351S;R851L‡
711+3A→G*	F508del*	I618N	R1066C	T388M
A1006E	F508del;R1438W‡	I618T	R1066G	T465I
A1025D	F575Y	I86M	R1066H*†	T501A
A1067P	F587I	I980K	R1070P	T582S
A1067T	F587L	K1060T	R1070Q	T908N
A1067V	F693L(TTG)	K162E	R1070W	T990I
A107G	F87L	K464E	R1162Q	V1008D

A1081V	F932S	K464N	R117C;G576A;R668C‡	V1010D
A1087P	G1047D	K522E	R117C†	V1153E
A120T	G1047R	K522Q	R117G	V11I
A1319E	G1061R	K951E	R117H*	V1240G
A1374D	G1069R	L1011S	R117L	V1293G
A141D	G1123R	L102R;F1016S‡	R117L;L997F‡	V1293I
A1466S	G1173S	L1065R	R117P	V1415F
A155P	G1237V	L1077P*†	R1239S	V201M
A234D	G1244E	L1227S	R1283G	V232A
A234V	G1244R	L1324P	R1283M	V232D
A238V	G1247R	L1335P	R1283S	V317A
A309D	G1249E	L137P	R1438W	V322M
A349V	G1249R	L1388P	R248K	V392G
A357T	G1265V	L1480P	R258G	V456A
A455E*†	G126D	L159S	R297Q	V456F
A455V	G1298V	L15P	R31L	V520I
A457T	G1349D	L15P;L1253F‡	R334L	V562I;A1006E‡
A462P	G149R;G576A;R668	L165S	R334Q	V562L
A46D	G178E	L167R	R334W	V591A
A534E	G178R	L206W*†	R347H*	V603F
A554E	G194R	L210P	R347L	V920L
A566D	G194V	L293P	R347P	V920M
A62P	G213E	L327P	R352Q	V93D
A872E	G213E;R668C‡	L32P	R352W	W1098C
c.1367_1369dupTTG	G213V	L333F	R516S	W1282G
C‡	G226R	L333H	R553Q	W1282R
C225R	G239R	L346P	R555G	W202C
C491R	G253R	L435S	R600S	W361R
C590Y	G27E	L441P	R709Q	W496R
C866Y	G27R	L453S	R74Q	Y1014C
D110E	G314E	L467F	R74Q;R297Q‡	Y1032C
D110H	G314R	L558F	R74Q;V201M;D1270N‡	Y1032N

D110N	G424S	L619S	R74W	Y1073C
D1152A	G437D	L633P	R74W;D1270N‡	Y1092H
D1152H*†	G461R	L636P	R74W;R1070W;D1270N‡	Y109H
D1270N*	G461V	L88S	R74W;S945L‡	Y109N
D1270Y	G463V	L927P	R74W;V201M;D1270N‡	Y122C
D1312G	G480C	L967F;L1096R‡	R74W;V201M;L997F‡	Y1381H
D1377H	G480D	L973F	R74W;V201M‡	Y161C
D1445N	G480S	M1101K*†	R751L	Y161D
D192G	G500D	M1137R	R75L	Y161S
D192N	G545R	M1137V	R75Q;L1065P‡	Y301C
D373N	G551A	M1210K	R75Q;N1088D‡	Y563N
D426N	G551D*	M150K	R75Q;S549N‡	Y89C
D443Y	G551R	M150R	R792G	Y913S
D443Y;G576A;R668C‡	G551S	M152L	R792Q	Y919C
D529G	G567A;R688C‡	M152V	R810G	
D565G	G576A;S1359Y‡	M265R	R851L	
D567N	G622D	M348K	R933G	
D579G	G622V	M394L	S1045Y	
D58H	G628A	M469V	S108F	
D58V	G628R	M498I	S1118F	
D614G	G85E*†	M952I	S1159F	
D651H	G930E	M952T	S1159P	
D651N	G970D	M961L	S1188L	
D806G	G970S	N1088D	S1251N	
D924N	G970V	N1195T	S1255P	
D979A	H1054D	N1303I	S13F	
D979V	H1079P	N1303K*	S13P	
D985H	H1085P	N186K	S158N	
D985Y	H1085R	N187K	S182R	
D993A	H1375N	N396Y	S18I	
D993G	H1375P	N418S	S18N	
D993Y	H139L	N900K	S308P	

E1104K	H139R	P1013H	S341P	
E1104V	H146R	P1013L	S364P	
E1126K	H199Q	P1021L	S434P	
E116K	H199Y	P1021T	S492F	
E116Q	H609L	P111L	S50P	
E1221V	H620P	P1372T	S519G	
E1228K	H620Q	P140S	S531P	
E1409K	H939R	P205S	S549I	
E1433K	H939R;H949L‡	P439S	S549N	
E193K	H954P	P499A	S549R*	
E217G	I1023R	P574H		

There are a very limited number of patients who harbour mutations not listed in Table 5 that may be responsive to Kaftrio. In these cases, Kaftrio can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision. This excludes patients with two Class I (null) mutations as they are unlikely to respond to modulator therapy (see section 4.4).

The individual diagnosis of CF should be based on diagnostic guidelines and clinical judgement as considerable variability exists in phenotype for patients harbouring the same genotype. For the classification of the CFTR mutations (dated September 2024), refer to the CFTR2 website for more information.

* Mutations supported by clinical data.

† Mutations supported by Real-World data in ≥ 5 patients.

‡ Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Non-annotated mutations are included based on the FRT assay in which a positive response is indicative of a clinical response with link to the EPAR.

Some CFTR mutations failed to reach the treshold CFTR mutants gaining a >10 pp increase in chloride transport upon incubation with Kalydeco or Kaftrio in the FRT test. Howver, some of these mutations showed a clinical response in vivo (see clinical efficacy)

Table 3 provides an overview of the CFTR mutation that did not show a positive response in the in vitro FRT test. These mutations are excluded from listing in section 5.1 of the SmPC

Table 3: CFTR mutations that did not show a positive response in the vitro FRT Assay

1234insACAAAA	C524R	I1398S	M1101R	S489P
1491-1500del	C832X	I148T;H609R	M1105R	T164P
149del84	D513G	I506S	M1137K	T465N
1949del84	D565E	I506T	M156R	T604I
2862delCAG	D572N	I507del	M1L	V1020E
2949del84	D579Y	I601T	M1T	V520F

3131del15	E815X	K95E	M1V	W1098R
3195del6	G1003E	L102P	M394R	W277X
3199del6	G149R	L102R	N1303K	W57G
4193T->G	G451V	L1065P	P99L	W57R
420del9	G458R	L127dup	Q1100P	Y109C
591del18	G85R	L137R	Q452P	Y517C
A1067D	G85V	L227R	R1066C	Y563D
A559E	G91R	L467P	R1066L	Y563H
A559P	G921E	L558S	R1066M	Y569C
A559T	H147del	L571S	R334W	Y569D
A559V	H147P	L594P	R516G	Y913C
A561E	H199R	L610S	R560G	Y914C
A613T	H609R	L617del	R560K	
A72D	I1005R	L73P	R560S	
c.1493-1507del15	I1234Vdel6aa	L927P	R560T	

2.2.3. Pharmacokinetics

No additional information provided.

2.2.4. Toxicology

No additional information provided.

2.2.5. Ecotoxicity/environmental risk assessment

Kaftrio consists of three active substances: ivacaftor (VX-770), tezacaftor (VX-661), and elexacaftor (VX-445). As part of the initial Marketing Authorization Application (MAA), Vertex submitted the following Environmental Risk Assessments for each active substance:

Ivacaftor

- Study VX-770-TX-084 (VX-770: Kalydeco Monotherapy and in Combination with VX-809 or VX-661 or VX-445 and VX-661. Environmental Phase I and II Risk Assessment, Report Amendment 1)

Tezacaftor

- Study VX-661-TX-062 (VX-661: ERA Phase I)
- Study VX-661-TX-070 (VX-661: ERA Phase II Tier A+B)

Elexacaftor

- VX-445-TX-031 (VX-445: ERA Phase I and Phase II Tier A)

As a result of the findings in the Phase II Tier A assessment, a Phase II Tier B assessment has been triggered.

As a post-marketing commitment, Vertex will perform a Phase II Tier B risk assessment for Elexacaftor in line with the EMA guideline on ERA (EMEA/CHMP/SWP/4447/00 corr 2). The results of the Phase II Tier B studies will be available by the end of Q2 2025.

The following studies with VX-445 (elexacaftor) will be conducted:

- Bioconcentration in Fish (OECD 305)
- Aerobic transformation in soil (OECD 307)
- Nitrogen Transformation (OECD 216)
- Terrestrial plants, seedling emergence and growth test (OECD 208)
- Acute Earthworm (by soil incorporation) (OECD 207)
- Reproduction, Earthworm (OECD 222)
- Inhibition of reproduction of Collembola (OECD 232)

No additional ERA studies, beyond the planned Phase II Tier B risk assessment for VX-445 (elexacaftor), have been submitted to support this submission.

2.2.1. 2.2.6. Discussion on non-clinical aspects

FRT Assay

The MAH has submitted Studies P289 and U032 in support of this application. A set of 235 CF-causing mutations was selected for Study P289, and this was further reduced to 219 mutations plus F508del that had the correct sequence and met the inclusion criteria for CFTR expression in the FRT assay. Next to *F508del*-CFTR, 175 of 218 mutations were responsive to the combination of ivacaftor, tezacaftor and elexacaftor, of which 127 mutations were identified to be responsive to the combination of tezacaftor and ivacaftor and 59 mutations were identified ivacaftor responsive. The remaining 43 were not responsive (not exceeding the 10pp threshold) to ivacaftor and/or tezacaftor and elexacaftor.

In study U032, 400 other CF mutations were tested in the FRT assay, of which 342 appeared responsive to the combination of ivacaftor, tezacaftor and elexacaftor in vitro.

The FRT cells are rat thyroid cells, that do normally not express a chloride conduction channel and therefore also do not express endogenous CFTR. This makes them useful for the test, but expressing CFTR in these cells is thus also considered an artificial system. Furthermore, only one allele is expressed in this FRT model, in contrast to the clinical situation in patients where two (different) forms of mutant CFTR are expressed. It should thus always be considered that with this system, the effect of the modulators on CFTR is a very isolated effect, which will not capture all clinical aspects of the disease. Therefore, it is considered that this test can be only indicative for the response in the clinic, but that it should not be used as exclusion criterium. Below some additional identified limitations of the FRT assay are discussed.

1. splice mutations

Certain mutations are not suitable for testing in this system as not all CFTR mutations can be generated at cDNA level (required for this test system), like splice mutations.

2. mutant CFTR expression level

It is considered that the efficacy of transfection with acceptation of levels of mRNA expression between 0.5-2-fold, seems wide. Therefore, the MAH was asked to discuss the influence of these different values in the results observed in chloride transport in vitro assay and clarify which of the proposed CFTR mutations are within the values between 1 and 2 and which ones have a value between 0.5 and 1. The MAH stated that the range from 0.5 to 2.0 is not influenced by the number of integrations, as the FlipIn system only allows one integration and implicitly states that this range is related to determination by RT-PCR. To get an impression of the relevance of mRNA and/or protein expression on the final performance of a certain mutant in the assay, the MAH was asked to provide the protein expression data with the mRNA expression data. These data were not provided as the MAH reasoned that total protein levels between different CFTR mutations could not be compared because many of the CFTR mutations result in processing and trafficking defects which cause premature degradation of the CFTR protein. Therefore the CHMP considered that differential mRNA expression levels were an indication for differential expression of the CFTR mutant form.

3. Deficiencies in acceptance criteria for cell line generation

qPCR data are used to in- or exclude a cell line from the FRT test. In case the average of 3 measurements is below 0.5-fold or higher than 2-fold the CFTR mRNA wildtype levels, a fourth measurement is conducted. In case that fourth measurement falls within the set boundaries, the cell line is accepted, passing the QC. Even when the average of the four assessments is outside the set boundaries. This is a very arbitrary type of quality control and could put a question mark to some of the accepted cell lines. For some of the mutations the generated cell line failed quality control. For these mutants, a second cell line will be made, and subjected again to analysis as part of study U032, which is supported.

4. Readout of FRT is qualitative, and not quantitative

Evaluation of chloride transport by means of Ussing chamber is not a quantitative assessment, and the magnitude of response in the FRT system does not correlate with the degree of clinical benefit. This statement from the MAH is supported. Therefore, the FRT system is not considered informative for assessing the relative benefit for different CFTR modulators. It is noted however the MAH did set a quantitative threshold of 10 pp increase, and the clinical relevance of this threshold is unclear (see point 5). However, the totality of existing clinical data shows that ELX/TEZ/IVA generally provides a superior treatment benefit over IVA monotherapy and TEZ/IVA combination therapy. It should be noted that CHMP does not support the conclusion that in all these cases Kaftrio would be more appropriate than Kalydeco or Symkevi, as additional modulators might also increase safety issues. Therefore, a decision on which modulators to use should be based on clinical efficacy and safety data primarily.

5. Clinical relevance of 10pp threshold

In addition to that, data on mRNA expression levels suggest overall a slightly lower level of mutant CFTR mRNA (< 1) as compared to wildtype CFTR mRNA (= 1) which could result in an underestimation of the performance on chloride transport of the mutants. Therefore, it is considered that CFTR mutants that perform lower than 10-pp threshold should not immediately be regarded as clinical not-responding mutations.

The paper published by Burgel et al, Lancet RM 2024 also indicates that 44-49% of the non-FDA indicated mutations do respond in the clinic upon use. '*17 variants were unequivocally responsive (always responsive in at least three responders homozygous or in trans with non-responsive variants), including nine FDA-approved variants (D1152H, G1249R, G551D, G85E, L206W, R347P, S549N, S945L, and S977F) and, importantly, eight non-FDA-approved variants (N1303K, R334W, R1066C, 2789+5G>A, 3272-26A>G, 3849+10kbC>T, c.3874-4522A>G and c.870-1113_870-1110del).*' Of these latter 8, N1303K, R1066C and R334W were included and did not perform well in the FRT assay study P289 (the

first two were even included as negative controls). This provides a strong indication that some non-responding mutations in the FRT assay may be false negatives with regard to prediction of the clinical meaningful response. It could thus be concluded that the restriction of the 10-percentage point threshold in the FRT assay can be superseded with clinical data, as it has been shown for the N1303K mutation. The multifactorial character of the disease requires clinical confirmation of the i*n vitro* results to investigate potential for quantitative improvement of lung function.

6. validation state of the FRT Assay

Upon request from CHMP for validation data of the assay, the MAH clarified which aspects were considered by the FDA during assay validation. These are listed below.

a) the comprehensive understanding of the consequences of individual CFTR mutations on CFTR channel function.

b) knowledge that the Ussing chamber in vitro electrophysiology measurement system is a standard and well-characterized method for evaluating ion flux across epithelial cell membranes with consistent, repeatable results.

c) data demonstrating mutant CFTR channels expressed in FRT cell lines were adequately validated.

d) confirmation that mature CFTR channels for each mutation were present in the epithelial cell membrane and, therefore, able to respond to ivacaftor.

e) FDA verification of in vitro data integrity and confirmation of in vitro findings on the basis of reconstruction of study results from raw data; and

f) consistency of in vitro assay findings with clinical efficacy data for mutations in which clinical data were available.

Although this summary of the FDA's assessment of the validity of the FRT assay might be relevant to the public, it makes it not possible for the CHMP to assess the validity of the FRT assay. The publication from the FDA only contains a reflection of their assessment and does not contain requested data to assess whether the FRT assay can be regarded valid for the purpose of use.

The summary of the FDA validation procedures provided by the MAH was not sufficiently informative for the CHMP to assess the validity of the FRT assay, and not all requested data was provided by the MAH. Therefore, based on the limited amount of validation information data, a conclusion on the reproducibility or validity of the assay cannot be made.

Conclusion

The differences in expression levels of different mutations, may provide under of over estimation of the results of certain mutants. That could influence the acceptance or the rejection of a certain mutant when the test result is close to the 10-pp threshold. Thereby, the inclusion criteria of the generated cell lines in the assay, as well as the 10-pp threshold are regarded too arbitrary. The FRT assay is not considered fully validated to predict clinical responsive and non-responsive mutations.

Overall, results obtained with the FRT assay are regarded not useable to exclude patients from therapy. Treatment with the modulators in patients carrying certain rare CFTR mutations should be followed by entering efficacy and safety data of this treatment in patient registries.

Considering the MAH proposal to rely on the *in vitro* FRT assay to define the patient population to be treated and the observed limitations of the FRT test, the CHMP decided to convey an Ad-Hoc Expert Group to discuss aspects related to the FRT test.

AHEG

The question posed to the Experts is detailed below:

Question 1: The Experts are invited to discuss whether for patients with rare (non-class I) CF causing mutations, clinical responsiveness to Kaftrio (e.g. FEV1 and SwCl) can be predicted based on in-vitro Fisher Rat Thyroid (FRT) assay (by means of an improvement of mature CFTR protein at the cell surface and at least a 10% increase in chloride transport) is sufficient to expect a clinical response in FEV1 and sweat chloride in vivo?

All experts agreed that the FRT assay has a high positive predictive value, based on the correlation from the presented clinical studies, real world data and publications. They were of the opinion that the FRT assay would give an indication of responsiveness but would not constitute a definite conclusive test. in addition, it cannot be used for complex mutations.

They were all in agreement that the FRT assay has limitations in relation to the negative predictive value (such as the N1303K mutation). In addition, the FTR test assess CFTR activity based on a single allele and cannot be used for every mutation (e.g. non-sense mutations) nor for complex alleles such as S1251N-F508C mutation.

The threshold used for the definition of positive response (10% increase over baseline in *in vitro* Cl^- transport when expressed as a percentage of normal (wildtype) CFTR Cl^- transport) was discussed. The experts acknowledged that there can be mutations that do not respond to the test (e.g. N1303K) and it is not known whether changing the threshold would be helpful in the predictability of the test.

Some experts mentioned that the FRT assay is not built to address the complexity of the genotype, the tissues involved and their complexity, therefore the test would not be predictive for some patients. Some positive response may be missed. Other models could be used (e.g. organoids) and would be desirable, so that they better take into account the complexity of the CFTR mutated genes and better mimic the human body such as organoids.

Conclusion from the AHEG:

The experts agreed that reliance on the in vitro FRT assay results without clinical data could be acceptable. Some experts mentioned however that confirmation with clinical data should be received after treatment.

The experts highlighted concerns on the acceptation of an indication based on the FRT assay performed only by the company. The fact that the test cannot be done in clinical practice, by an independent body or treating hospital was an issue for all experts including patient representatives.

Final CHMP conclusion on FRT assay.

The CHMP having considered all available evidence and above AHEG recommendations was on the view that a positive result in the FRT assay could be seen as indicative for providing a response upon clinical treatment for a tested CFTR variant. However, a negative result in the FRT is not regarded indicative for treatment failure in patient carrying that tested CFTR mutant. Therefore, it is emphasized that patients carrying mutants not tested in the FRT assay should ideally not be excluded as they may carry a mutation responsive to Kaftrio.

Other in vitro assays

The MAH provided information on two type of assays that are patient derived and could investigate the response of E/T/I on CFTR splicing mutants. The MAH referred to CF human bronchial epithelial (HBE) cells and organoids. Next to these in vitro systems, also human nasal epithelial cells have been used in

the public domain with good results (Ensink[7], Laselva[8] and Veit[9], see below). Although the latter being patient derived, the acquisition of these cells seem less invasive and could be a promising system for patient derived and patient specific analysis of the effect of E/T/I on CFTR (splicing) mutants.

ERA

For elexacaftor, the MAH is currently conducting studies to complete the Phase II Tier B risk assessment to fulfil a post-marketing commitment and studies will be available by the end of Q2 2025. The MAH considers that this extension of indication would not influence the submitted prevalence data and consequently would not translate into other increase in environmental exposure to ivacaftor (VX-770), tezacaftor (VX-661), or elexacaftor (VX-445). This can be agreed by CHMP considering the rarity of the mutations.

2.2.2. Conclusion on the non-clinical aspects

The in-vitro FRT assay has a number of limitations. The test is regarded of qualitative but not of quantitative value. In conclusion, it is not considered fully validated to establish clinical responsive and non-responsive mutations as it is not 100% fully correlated with clinical response. Therefore, it was considered that the output of the FRT assay gives an indication for the clinical anticipated effect of the various (combinations of) CFTR modulators on CFTR maturation and chloride transport of CFTR mutants on a molecular basis. Performance of the CFTR mutant above the 10-pp threshold in the FRT assay could be indicative of a clinical meaningful response. However, performance of the CFTR mutant below the 10-pp threshold is not considered predictive for absence of a clinical meaningful response.

The extended indication does not lead to a significant increase in environmental exposure. Considering the above data, ivacaftor, tezacaftor or elexacaftor is not expected to pose a risk to the environment.

However, the MAH is requested to fulfil the post marketing commitment about elexacaftor. The ERA studies will be available by end of Q2 2025.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The WSA has provided a statement to the effect that clinical trials conducted outside the community were

[7] Ensinck MM, De Keersmaecker L, Ramalho AS, Cuyx S, Van Biervliet S, Dupont L, Christ F, Debyser Z, Vermeulen F, Carlon MS. Novel CFTR modulator combinations maximise rescue of G85E and N1303K in rectal organoids. ERJ Open Res. 2022 Apr 19;8(2):00716-2021. doi: 10.1183/23120541.00716-2021. PMID: 35449760; PMCID: PMC9016267.

[8] Laselva O, Bartlett C, Gunawardena TNA, Ouyang H, Eckford PDW, Moraes TJ, Bear CE, Gonska T. Rescue of multiple class II CFTR mutations by elexacaftor+tezacaftor+ivacaftor mediated in part by the dual activities of elexacaftor as both corrector and potentiator. Eur Respir J. 2021 Jun 17;57(6):2002774. doi: 10.1183/13993003.02774-2020. PMID: 33303536; PMCID: PMC8209484.

[9] Veit G, Roldan A, Hancock MA, Da Fonte DF, Xu H, Hussein M, Frenkiel S, Matouk E, Velkov T, Lukacs GL. Allosteric folding correction of F508del and rare CFTR mutants by elexacaftor-tezacaftor-ivacaftor (Trikafta) combination. JCI Insight. 2020 Sep 17;5(18):e139983. doi: 10.1172/jci.insight.139983. PMID: 32853178; PMCID: PMC7526550.

carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Overview of clinical studies

Efficacy of ELX/TEZ/IVA for patients with CF and at least 1 ELX/TEZ/IVA-responsive, nonF508del CFTR mutations is supported by clinical study, noninterventional RWE, and/or in vitro data:

1. Randomized, placebo-controlled clinical study data in subjects with 18 of the most common ELX/TEZ/IVA-responsive, non-F508del CFTR mutations (Study 124) and Week 4 data from the open-label extension study (Study 125);

2. Noninterventional RWE data from US patients with ELX/TEZ/IVA-responsive, non-F508del CFTR mutations receiving commercially available ELX/TEZ/IVA (Study CFD-016);

3. Clinical evidence from a recently presented study at the North American CF Conference and 2 published studies in people with CF who have an N1303K mutation.

2.3.2. Pharmacokinetics

Pharmacokinetics of ELX/TEZ/IVA in cystic fibrosis subjects 6 years of age and older with a non-*F508del* ELX/TEZ/IVA-responsive CFTR mutation was evaluated in study VX21-445-124 (Study 124). The ELX/TEZ/IVA dosing regimen was based on the subject's age and weight on Day 1 as shown in **Table *4*** Subjects received the same dose of ELX/TEZ/IVA throughout the treatment period, regardless of change in age or weight.

Table 4: Study 124 Treatment Period Dosages.

Treatment Group Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
ELX/TEZ/IVA			
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h
≥6 to <12 years			
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
<30 kg	100 mg qd	50 mg qd	75 mg q12h
Placebo			
All ages and all weights	0 mg	0 mg	0 mg

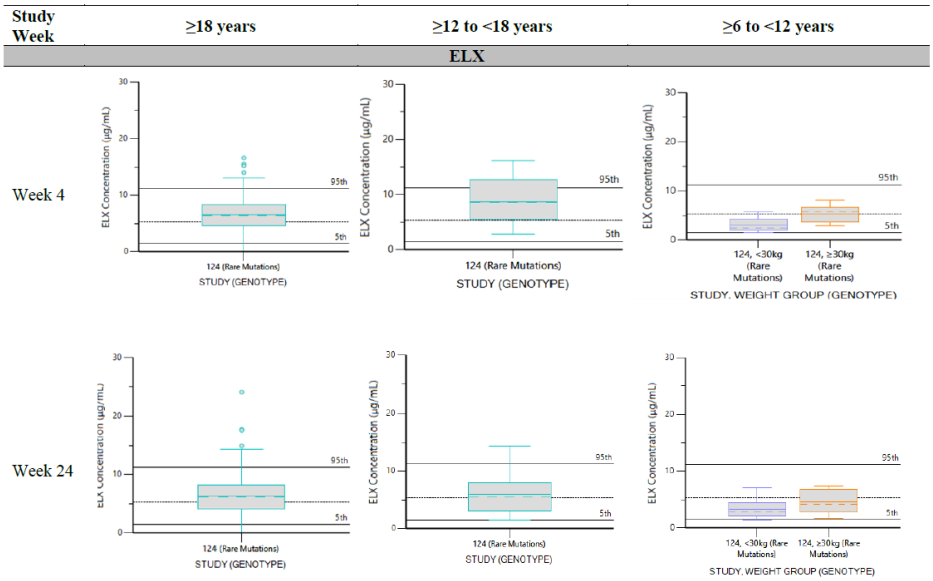
ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Blood samples were collected at Day 1 and at Weeks 4 and 24 Visits (±5 days) to determine plasma concentrations of ELX, TEZ, IVA, and their relevant metabolites. Trough concentrations were analyzed and summarized as the only PK parameter. ELX and its major metabolite (M23-ELX), TEZ and its major metabolite (M1-TEZ), and IVA and its major metabolite (M1-IVA) were quantitated using validated LC-MS/MS methods.

Pharmacokinetic data was evaluated in 155/154 (Week 4/24), 18/19 (Week 4/24), 9/9 (Week 4/24) and 14/14 (Week 4/24) in subjects ≥ 18 years, ≥ 12 to < 18 years, ≥ 6 to < 12 years with ≥ 30 kg and ≥ 6 to < 12 years with < 30 kg, respectively.

Figure 2: Boxplots of Predose Plasma Concentrations (Ctrough) at Weeks 4 and 24 by Age Group (and Weight Group for ELX).

Results

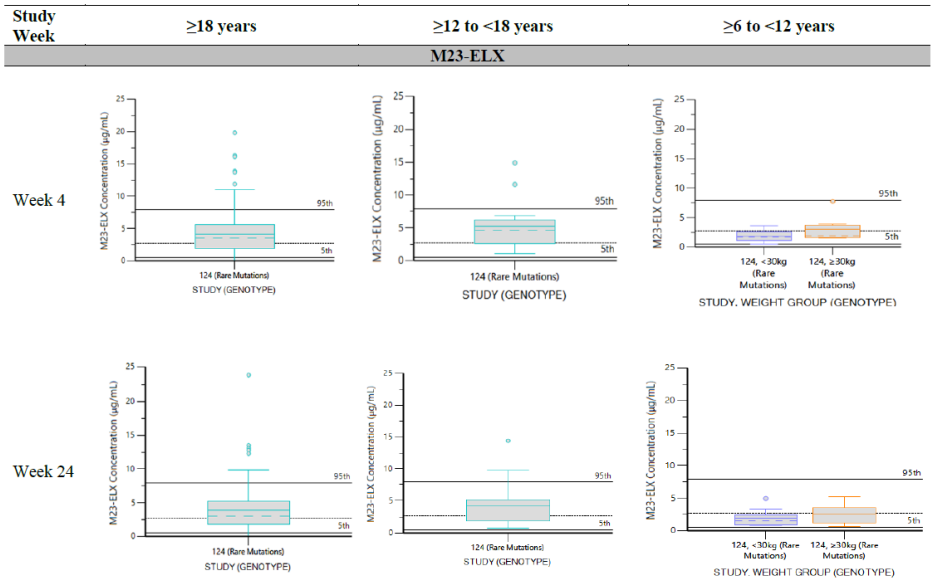


Source: Figure 14.4.2.1

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; M1-IVA: hydroxymethyl-ivacaftor, metabolite of ivacaftor; M1-TEZ: metabolite of tezacaftor; M23-ELX: metabolite of elexacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; yo: years old.

Notes: Subjects received ELX/TEZ/IVA based on their age and weight on Day 1 and throughout the treatment period regardless of change in age or weight as described in Table 9-1. The dose for the ≥6 to <12 years old, <30 kg CF population was ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. For all others, the dose was ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. The dashed horizontal line represents the median of the adult concentration values (across studies VX17-445-102, VX17-445-103, and VX18-445-104) and the top ('95th') and bottom ('5th') solid horizontal lines indicate the 5th and 95th percentiles of the adult values (VX17-445-102, VX17-445-103, and VX18-445-104). In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers were plotted as outliers (markers outside of the whiskers).

Figure 3: Boxplots of Predose Plasma Concentrations (Ctrough) at Weeks 4 and 24 by Age Group (and Weight Group for M23-ELX).

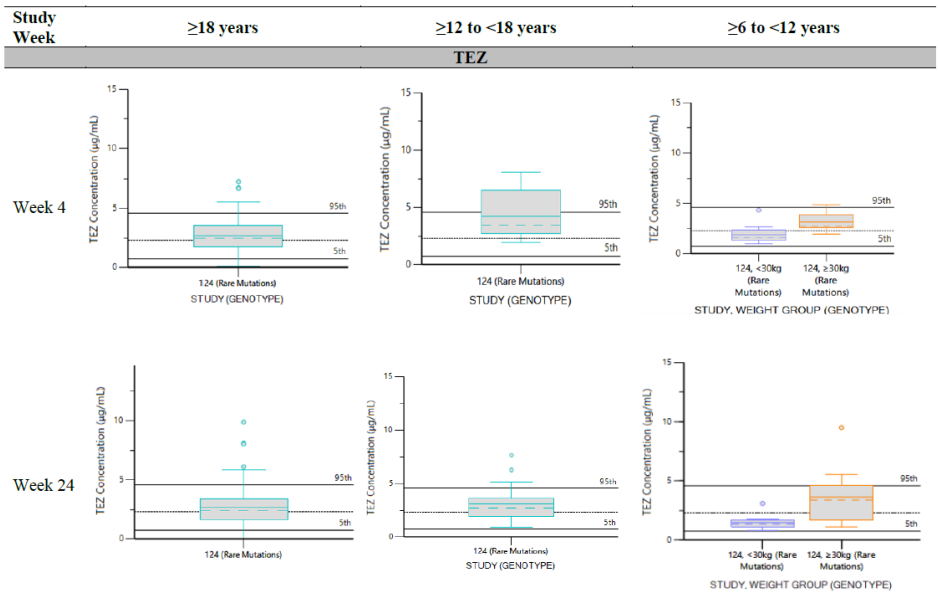


Source: Figure 14.4.2.1

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; M1-IVA: hydroxymethyl-ivacaftor, metabolite of ivacaftor; M1-TEZ: metabolite of tezacaftor; M23-ELX: metabolite of elexacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; yo: years old.

Notes: Subjects received ELX/TEZ/IVA based on their age and weight on Day 1 and throughout the treatment period regardless of change in age or weight as described in Table 9-1. The dose for the ≥6 to <12 years old, <30 kg CF population was ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. For all others, the dose was ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. The dashed horizontal line represents the median of the adult concentration values (across studies VX17-445-102, VX17-445-103, and VX18-445-104) and the top ('95th') and bottom ('5th') solid horizontal lines indicate the 5th and 95th percentiles of the adult values (VX17-445-102, VX17-445-103, and VX18-445-104). In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers were plotted as outliers (markers outside of the whiskers).

Figure 4: Boxplots of Predose Plasma Concentrations (Ctrough) at Weeks 4 and 24 by Age Group (and Weight Group for TEZ).

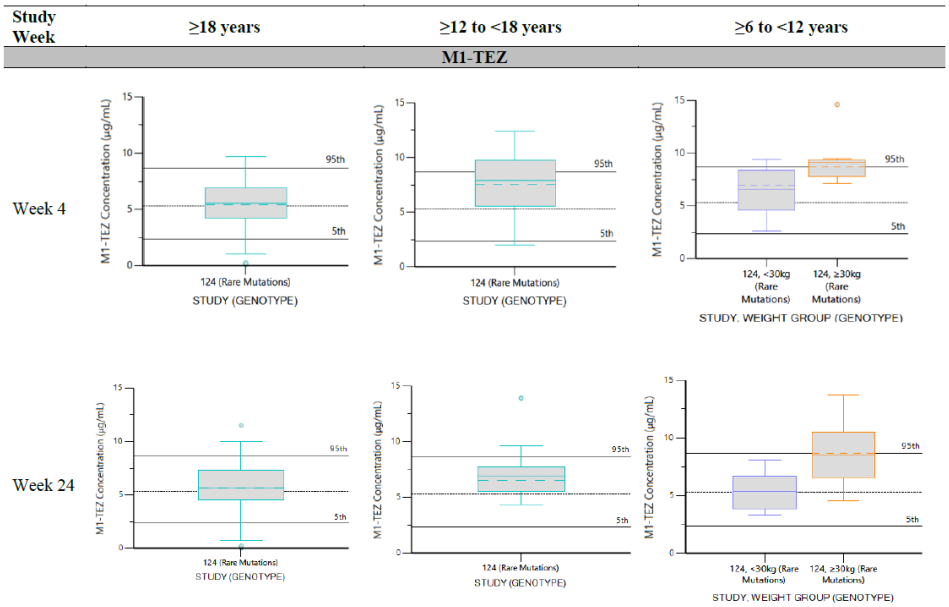


Source: Figure 14.4.2.1

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; M1-IVA: hydroxymethyl-ivacaftor, metabolite of ivacaftor; M1-TEZ: metabolite of tezacaftor; M23-ELX: metabolite of elexacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; yo: years old.

Notes: Subjects received ELX/TEZ/IVA based on their age and weight on Day 1 and throughout the treatment period regardless of change in age or weight as described in Table 9-1. The dose for the ≥6 to <12 years old, <30 kg CF population was ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. For all others, the dose was ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. The dashed horizontal line represents the median of the adult concentration values (across studies VX17-445-102, VX17-445-103, and VX18-445-104) and the top ('95th') and bottom ('5th') solid horizontal lines indicate the 5th and 95th percentiles of the adult values (VX17-445-102, VX17-445-103, and VX18-445-104). In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers were plotted as outliers (markers outside of the whiskers).

Figure 5: Boxplots of Predose Plasma Concentrations (Ctrough) at Weeks 4 and 24 by Age Group (and Weight Group for M-1 TEZ).

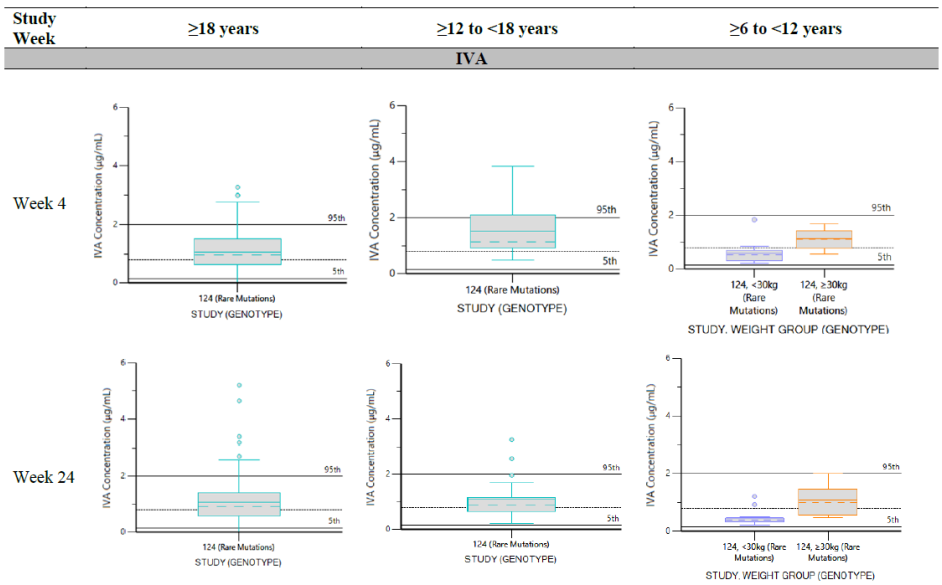


Source: Figure 14.4.2.1

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; M1-IVA: hydroxymethyl-ivacaftor, metabolite of ivacaftor; M1-TEZ: metabolite of tezacaftor; M23-ELX: metabolite of elexacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; yo: years old.

Notes: Subjects received ELX/TEZ/IVA based on their age and weight on Day 1 and throughout the treatment period regardless of change in age or weight as described in Table 9-1. The dose for the ≥6 to <12 years old, <30 kg CF population was ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. For all others, the dose was ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. The dashed horizontal line represents the median of the adult concentration values (across studies VX17-445-102, VX17-445-103, and VX18-445-104) and the top ('95th') and bottom ('5th') solid horizontal lines indicate the 5th and 95th percentiles of the adult values (VX17-445-102, VX17-445-103, and VX18-445-104). In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers were plotted as outliers (markers outside of the whiskers).

Figure 6: Boxplots of Predose Plasma Concentrations (Ctrough) at Weeks 4 and 24 by Age Group (and Weight Group for IVA).



Source: Figure 14.4.2.1

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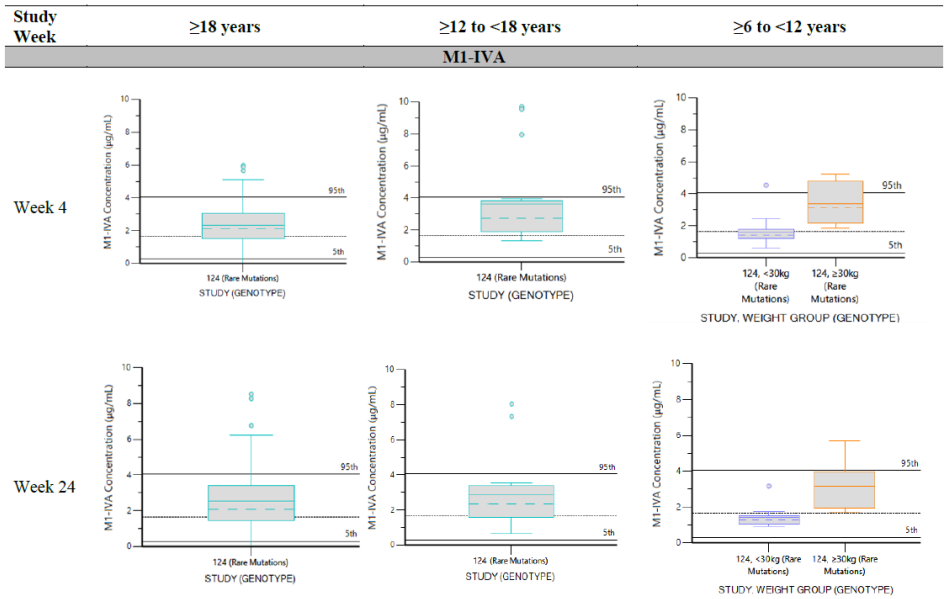
Notes: Subjects received ELX/TEZ/IVA based on their age and weight on Day 1 and throughout the treatment period regardless of change in age or weight as described in Table 9-1. The dose for the ≥6 to <12 years old, <30 kg CF population was ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. For all others, the dose was ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. The dashed horizontal line represents the median of the adult concentration values (across studies VX17-445-102, VX17-445-103, and VX18-445-104) and the top ('95th') and bottom ('5th') solid horizontal lines indicate the 5th and 95th percentiles of the adult values (VX17-445-102, VX17-445-103, and VX18-445-104). In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers were plotted as outliers (markers outside of the whiskers).

Figure 7: Boxplots of Predose Plasma Concentrations (Ctrough) at Weeks 4 and 24 by Age Group (and Weight Group for M1-IVA).



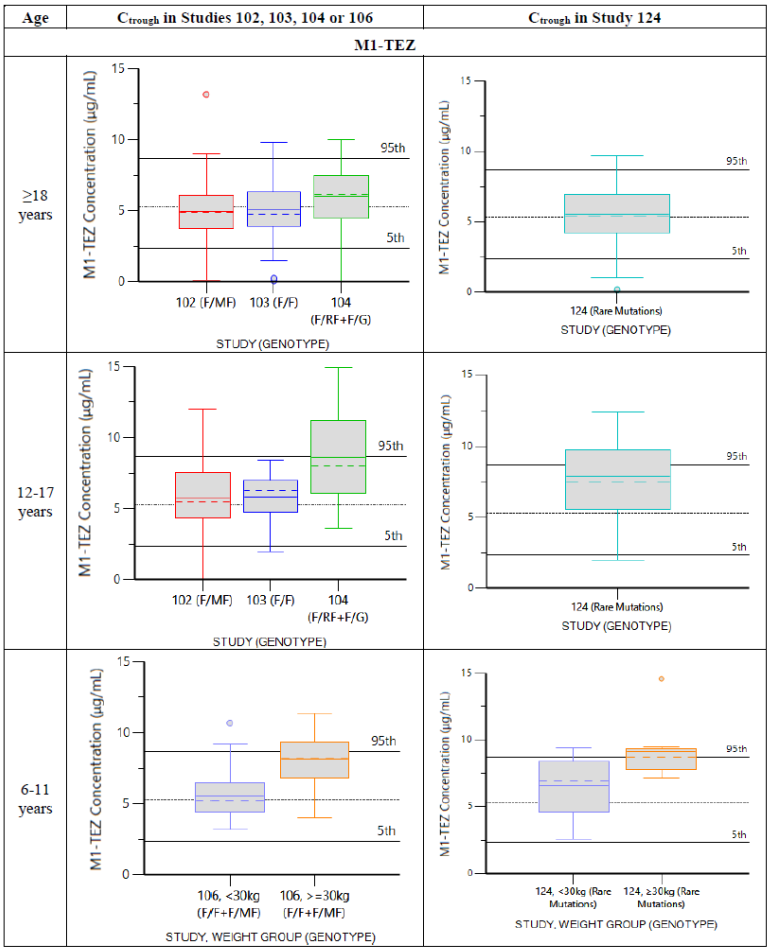
Source: Figure 14.4.2.1

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; M1-IVA: hydroxymethyl-ivacaftor, metabolite of ivacaftor; M1-TEZ: metabolite of tezacaftor; M23-ELX: metabolite of elexacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; yo: years old.

Notes: Subjects received ELX/TEZ/IVA based on their age and weight on Day 1 and throughout the treatment period regardless of change in age or weight as described in Table 9-1. The dose for the ≥6 to <12 years old, <30 kg CF population was ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. For all others, the dose was ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. The dashed horizontal line represents the median of the adult concentration values (across studies VX17-445-102, VX17-445-103, and VX18-445-104) and the top ('95th') and bottom ('5th') solid horizontal lines indicate the 5th and 95th percentiles of the adult values (VX17-445-102, VX17-445-103, and VX18-445-104). In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers were plotted as outliers (markers outside of the whiskers).

The exposures across the age groups were consistent with adult exposures previously observed in ELX/TEZ/IVA studies (Studies 102, 103, and 104), as the majority of the exposures generally fell within the adult exposure range. The exposures were also similar between Weeks 4 and 24. M1-TEZ exposures observed in subjects ≥6 to <12 years of age weighing ≥30 kg who received the adult dose trended higher as compared to adult exposure levels. However, these exposures are similar to M1-TEZ exposures for the same age and weight group in Study 106 (see **Figure *8*** below).

Figure 8: Boxplots of Predose Plasma Concentrations (Ctrough) at Week 4 for Analytes in Studies 102, 103, 104, 106 and 124 for Different Age Groups (and Weight Groups for CF Subjects 6 Through 11 Years of Age).



Source: Report T368 and VX21-445-124 CSR/Figure 14.4.2.1
CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; M1-IVA: M1 metabolite of ivacaftor; M1-TEZ: M1 metabolite of tezacaftor; M23-ELX: M23 metabolite of elexacaftor; TEZ: tezacaftor
Notes: In the box plots, the dashed and solid lines represent the median and arithmetic mean, respectively; the ends of the box are the 25th (first quartile) and 75th percentiles (third quartile). The lower and upper whiskers extend to the lowest and highest data value still within 1.5 times interquartile range (the middle 50%) of the first and third quantile. Data values that do not fall between the whiskers are plotted as outliers (markers outside of the whiskers). The dashed horizontal line represents the median of the adult values (across Studies 102, 103, and 104) and the top ('95th') and bottom ('5th') solid horizontal lines indicates the 5th and 95th percentiles of the adult values (across Studies 102, 103, and 104). Rare mutation in the plot refers to ETI-responsive, non-F mutation.

2.3.3. Pharmacodynamics

NA

2.3.4. PK/PD modelling

NA

2.3.5. Discussion on clinical pharmacology

The majority of exposures for all analytes for all age and weight groups generally fall within the 5th and 95th percentiles of the exposures observed in CF subjects ≥18 years of age in previous ELX/TEZ/IVA studies (the adult exposure range in Study 102, 103 and 104), with the exception of M1-TEZ exposures for subjects ≥6 to <12 years of age weighing ≥30 kg who received the adult dose. These exposures however are similar to M1-TEZ exposures for the same age and weight group in Study 106 and thus they are not expected to be clinically relevant.

2.3.6. Conclusions on clinical pharmacology

The exposures of ELX, M23-ELX, TEZ, M1-TEZ, IVA and M1-IVA were similar between Weeks 4 and 24 and were also consistent with adult exposures previously observed in ELX/TEZ/IVA studies. The exposure for M1-TEZ for subjects ≥6 to <12 years of age weighing ≥30 was slightly higher than previously observed adult concentration, but similar as in study 106 for the same age and weight group.

2.4. Clinical efficacy

With reference to the initial MAA EMEA/H/C/005269, the core efficacy data included in the clinical development programme were obtained from two controlled Phase 3 studies:

- Study 102: a 24-week double-blind placebo-controlled study in subjects with a single *F508del* allele and a minimal function mutation (F/MF)
- Study 103: a 4-week double-blind active-controlled study in subjects with two *F508del* alleles (F/F). The comparator was TEZ/IVA.

Supportive efficacy data are from:

- Phase 1/2 Study 001 in F/MF (Part D) and F/F subjects (Part E)

Study 105, an open-label extension (OLE) study evaluating long-term safety and efficacy for 192 weeks in subjects who participated in Studies 102 and 103 The Applicant has submitted new data from two clinical studies (study VX21-445-124 and the Open label extension study VX21-445-125) and one observational study (study VX22-CFD-016) to demonstrate the benefit/risk profile for patients with CF and 1 of 183 ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations. Eligible mutations were selected based on (a) *in vitro* responsiveness to ELX/TEZ/IVA in a panel of Fischer Rat Thyroid (FRT) cells individually expressing rare missense mutations or (b) splice mutations that produce reduced amounts of normal CFTR protein and have been previously shown to respond to IVA and TEZ/IVA in clinical studies (i.e., non-canonical splice mutations) and are therefore expected to also be responsive to ELX/TEZ/IVA. Because it is not feasible to test every rare mutation in a clinical study, not all of the 183 mutations were represented in the studies.

In addition to these three studies, clinical data from three investigator-initiated studies are included to demonstrate that patients with at least one *N1303K* mutation can derive clinical benefit from ELX/TEZ/IVA treatment. The *N1303K* mutation is one of the more common rare mutations, which is not included in the list of FRT-responsive mutations.

2.4.1. Main study

VX21-445-124: a Phase 3, Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-F508del ELX/TEZ/IVA-responsive CFTR Mutation.

Methods

Design

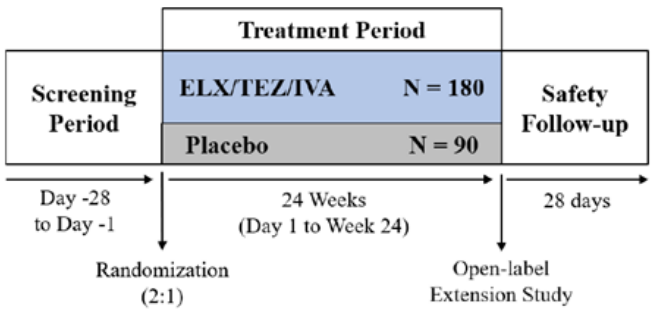
Study 124 was a Phase 3 randomised, placebo-controlled, double-blind, parallel group study with a duration of 24 weeks.

Subjects were randomised 2:1 (ELX/TEZ/IVA: placebo), with approximately 180 subjects planned in the ELX/TEZ/IVA group and approximately 90 subjects planned in the placebo group.

Randomisation was stratified based on ppFEV1 determined during the Screening Period (<70% versus ≥70), age at the Screening Visit (<18 years old versus ≥18 years old), and CFTR genotype (contains ≥1 RF-like mutation versus does not contain an RF-like mutation).

A schematic of the study design is shown in **Figure *9***.

Figure 9: Study 124 design



Source: Study 124 Protocol Version 3.0
ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

Study participants

Study participants were included based on the following criteria:

CFTR genotype: at least 1 of 18 ELX/TEZ/IVA responsive, non-*F508del* CFTR mutations (listed in

- **Table *5***).
- ppFEV1 at screening: an FEV1 value ≥40% and ≤100% of predicted mean for age, sex and height (according to the equations of the Global Lung Function Initiative [GLI]). Up to 10% of subjects were to be enrolled with a screening ppFEV1 value >90% and ≤100%.
- Age: ≥6 years of age.

Table 5: ELX/TEZ/IVA-responsive CFTR mutations eligible for Studies 124 and 125

RF-like mutations				MF-like mutations
Splice mutations	FRT-responsive mutations			FRT-responsive mutations
2789+5G>A	*P5L*	*T338I*	*L997F*	*G85E*
3272-26A>G	*R117C*	*R347H*	*R1066H*	*R347P*
3849+10kbC>T	*L206W*	*A455E*	*D1152H*	*L1077P*
	V232D	*S945L*		*M1101K*

Sources: Study 124 CSR/Table 9-2

ELX: elexacaftor; FRT: Fischer rat thyroid; IVA: ivacaftor; MF: minimal function; RF: residual function; TEZ: tezacaftor

Note: MF-like mutations have a clinical phenotype without evidence of residual CFTR function. RF-like mutations result in residual CFTR function. "FRT-responsive mutations" are mutations that are considered responsive to ELX/TEZ/IVA based on evidence from the FRT cell system. "Splice mutations" include non-canonical splice mutations that are predicted to result in a small quantity of functional CFTR protein.

Excluded from participation were:

- Subjects harbouring one of the following exclusionary mutations: *F508del*, *S549N*, *G551S*, *S1255P*, *R117H*, *S549R*, *G1244E*, *G1349D*, *G178R*, *G551D*, *S1251N*.
- Pregnant and nursing women.
- Subjects with a history of any illness or condition that could have confounded the study results or posed an additional safety risk (e.g., clinically significant hepatic cirrhosis with or without portal hypertension).
- Subjects with an acute upper or lower respiratory infection or findings suggestive of a pulmonary exacerbation (PEx) or changes in medical regimen for their pulmonary disease within 28 days before the first dose of study drug.
- Subjects with protocol-defined laboratory values at screening indicative of abnormal liver or renal function.

Treatments

The treatments consisted of ELX/TEZ/IVA or placebo.

ELX/TEX/IVA dosing regimen was based on the subject's age and weight on Day 1, following the approved posology for patients with at least one *F508del* mutation. Subjects received the same dose throughout the Treatment Period.

Endpoints

The primary efficacy endpoint was absolute change from baseline in ppFEV1 through Week 24. Secondary efficacy endpoints were absolute changes from baseline through Week 24 in sweat chloride (SwCl), Cystic Fibrosis Questionnaire – Revised Respiratory Domain (CFQ-R RD) score, BMI, and Weight, and Number of PEx through Week 24. For subjects ≤20 years of age, BMI and Weight z-scores through Week 24 were also evaluated to correct for changes in BMI and Weight because of growing older.

Assessments

Spirometry was performed according to the internationally recognised American Thoracic Society Guidelines[10] and ppFEV1 was calculated using GLI standards.

[10] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) was used to capture and evaluate the impact of ELX/TEZ/IVA on patient-reported respiratory symptoms and other aspects of health-related quality of life. A difference of at least 4 points in the respiratory domain (RD) score of the CFQ-R is considered the minimum clinically important difference.

Pex was defined as a clinical deterioration in respiratory status necessitating a change in antibiotic therapy (intravenous [IV], inhaled, or oral) for any 4 or more of the following signs or symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38°C (equivalent to approximately 100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection.

Statistical methods

Models

Analysis of the primary efficacy endpoint of absolute change from baseline in ppFEV$_1$ was performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model included treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV1, age at screening (<18 versus ≥18 years of age) and mutation group (contains ≥1 RF-like mutation versus does not contain an RF-like mutation) as covariates. A similar MMRM approach was used for all secondary endpoints (SwCl, CFQ-R RD score, BMI, Weight, BMI z-score, Weight z-score), except for Pex, which used a negative binomial regression model with a fixed effect for treatment, as well as continuous baseline ppFEV1, age at screening (<18 versus ≥18 years of age) and mutation group (contains ≥1 RF-like mutation versus does not contain an RF-like mutation) as covariates.

Multiplicity adjustment of secondary endpoints

Study 124 included a hierarchical testing procedure to control the type I error rate for the multiple key secondary endpoints which were tested at an alpha of 0.05. For a test at any step to be considered statistically significant within the testing hierarchy, it must have been statistically significant, and all previous tests (if any) within the hierarchy must have been statistically significant at the 0.05 level.

Sensitivity analysis

For the primary endpoint, a multiple imputation algorithm was used to assess the impact of missing data and the assumption that data are missing at random. Only missing values were imputed for which all subsequent visits were missing too. Missing single data points (between two non-missing data points) were not imputed. For participants with missing absolute change from baseline in ppFEV1 at the last timepoint of the dependent variable (Week 24), who discontinued treatment because of Aes, noncompliance with study drug, death, or physician decision, or because the subject refused further dosing or required prohibited medication the imputed value was drawn from a distribution with a mean value of the lower 25 percentile of the absolute change values from baseline at each relevant timepoint, for each treatment arm. For participants with missing absolute change from baseline in ppFEV1 at the last timepoint of the dependent variable (Week 24), who completed the protocol-specified treatment or discontinued treatment for any reason not listed in Category 1, the imputed values were drawn from the overall mean at the relevant timepoints for each treatment arm.

An MMRM analogous to that for the analysis of the primary endpoint was then applied to each imputed dataset and the estimates pooled using the standard multiple imputation approach with between and within imputation variability taken into account.

Results

Participant flow

Of the 307 subjects who received at least 1 dose of study drug, 9 (2.9%) subjects (all in the ELX/TEZ/IVA group) prematurely discontinued treatment (5 due to an AE, 2 due a pregnancy, 2 refused further dosing).

Conduct of the study

The study was conducted between 09 May 2022 and 05 July 2023 in 84 centres in Europe and Canada.

The original protocol was dated 12 October 2021 and included two major amendments.

The first major amendment (dated 24 January 2022) expanded the list of eligible mutations from 8 to 18. The following mutations were added: *P5L*, *R117C*, *V232D*, *T338I*, *R347H*, *S945L*, *L997F*, *R1066H* (all RF), *L1077P* and *M1101K* (both MF).

The second amendment (dated 21 April 2022) expanded the range of qualifying ppFEV1 values.

Protocol deviations

A total of 27 (8.8%) subjects had an important protocol deviation (IPD), related to study conduct (13 subjects), eligibility criteria (5), study drug (5), informed consent (2), SAE criteria (2) and prohibited medication (1). The number of IPD was balanced between the two treatment groups.

Baseline data

In general, demographic (Table 6) and baseline characteristics (Table 7) were balanced between the two treatment groups.

A total of 307 subjects were included, comprising 142 (46.3%) males and 165 (53.7%) females. The mean (SD) age at baseline was 33.5 (16.0) years and most subjects were white (n = 259 [84.4%]) and from Europe (n = 183 [92%]). The study included 66 (48.9%) subjects <18 years.

At baseline, the mean (SD) Weight was 62.4 (17.9) kg, mean (SD) Height 164.8 (14.3) cm and mean (SD) BMI was 22.46 (4.45) kg/m2. The mean (SD) FEV1 was 67.7 (17.7) % predicted and the mean SwCl 78.1 (27.5) mmol/L. A total of 22% of patients had a baseline SwCl < 60mmol/L.

Most subjects harboured a CFTR mutation that included ≥1 RF mutation (n = 225 [73.3%]) while 82 (26.7%) harboured a non-RF mutation. A total of 38.1% of patients suffered from pancreatic failure.

Table 6: Study 124 subject demographics (FAS)

Demographic	Placebo N = 102	ELX/TEZ/IVA N = 205	Total N = 307
Sex, n (%)			
Male	50 (49.0)	92 (44.9)	142 (46.3)
Female	52 (51.0)	113 (55.1)	165 (53.7)
Childbearing potential[a], n (%)			
Yes	37 (71.2)	93 (82.3)	130 (78.8)
No	15 (28.8)	20 (17.7)	35 (21.2)
Age at baseline (years)			
n	102	205	307
Mean (SD)	33.9 (16.4)	33.3 (15.9)	33.5 (16.0)
Median	33.5	33.4	33.4
Min, max	7.0, 87.3	6.3, 73.2	6.3, 87.3
Ethnicity, n (%)			
Hispanic or Latino	3 (2.9)	8 (3.9)	11 (3.6)
Not Hispanic or Latino	88 (86.3)	171 (83.4)	259 (84.4)
Not collected per local regulations	11 (10.8)	26 (12.7)	37 (12.1)
Race, n (%)			
White	87 (85.3)	172 (83.9)	259 (84.4)
Black or African American	0	0	0
Asian	3 (2.9)	4 (2.0)	7 (2.3)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	1 (1.0)	3 (1.5)	4 (1.3)
Not collected per local regulations	12 (11.8)	26 (12.7)	38 (12.4)
Geographic Region, n (%)			
North America	10 (9.8)	14 (6.8)	24 (7.8)
Europe	92 (90.2)	191 (93.2)	283 (92.2)

Source: Module 2.7.3/Table 7

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 (scheduled or unscheduled) before the first dose of study drug. If a subject was reported to have multiple races, then the subject was counted for each race reported. Asian category includes: Northeast Asian, Southeast Asian, Other Asian, and Asian, Region Not Reported.

[a] Percentages of childbearing women were based on the number of women in the FAS.

Table 7: Study 124 baseline characteristics (FAS)

Characteristic	Placebo N = 102	ELX/TEZ/IVA N = 205	Total N = 307
Weight (kg)			
n	102	205	307
Mean (SD)	63.2 (16.7)	61.9 (18.5)	62.4 (17.9)
Height (cm)			
n	102	205	307
Mean (SD)	166.2 (13.6)	164.2 (14.7)	164.8 (14.3)
BMI (kg/m^2)			
n	102	205	307
Mean (SD)	22.48 (4.16)	22.45 (4.60)	22.46 (4.45)
BMI z-score (subjects ≤20 years old at baseline)			
n	26	52	78
Mean (SD)	-0.22 (1.01)	-0.34 (1.04)	-0.30 (1.03)
Weight z-score (subjects ≤20 years old at baseline)			
n	26	52	78
Mean (SD)	-0.29 (1.15)	-0.39 (1.18)	-0.36 (1.16)
Age group (in years) at the Screening Visit, n (%)			
<18	20 (19.6)	44 (21.5)	64 (20.8)
≥18	82 (80.4)	161 (78.5)	243 (79.2)
$ppFEV_1$ category at the Screening Visit, n (%)			
<70	50 (49.0)	100 (48.8)	150 (48.9)
≥70	52 (51.0)	105 (51.2)	157 (51.1)
$ppFEV_1$ category at baseline, n (%)			
<40	5 (4.9)	5 (2.4)	10 (3.3)
≥40 to <70	47 (46.1)	99 (48.3)	146 (47.6)
≥70 to ≤90	38 (37.3)	78 (38.0)	116 (37.8)
>90	12 (11.8)	23 (11.2)	35 (11.4)
CFTR mutation group, n (%)			
Contains ≥1 RF-like mutation	74 (72.5)	151 (73.7)	225 (73.3)
Does not contain an RF-like mutation	28 (27.5)	54 (26.3)	82 (26.7)
$ppFEV_1$			
n	102	205	307
Mean (SD)	68.1 (18.1)	67.5 (17.6)	67.7 (17.7)
SwCl (mmol/L)			
n	100	202	302
Mean (SD)	75.2 (28.7)	79.5 (26.9)	78.1 (27.5)
CFQ-R RD score at baseline			
n	102	202	304
Mean (SD)	65.8 (21.3)	64.1 (20.7)	64.7 (20.9)

Source: Module 2.7.3/Table 8

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug.

Concomitant medications

Concomitant medication was defined as medication that was continued or newly received during the Treatment Period. The most common concomitant medications (incidence of at least 20% of total subjects) were medications typically used for management of CF and two common pain medications. Concomitant medications were generally balanced between the two treatment groups.

Numbers analysed

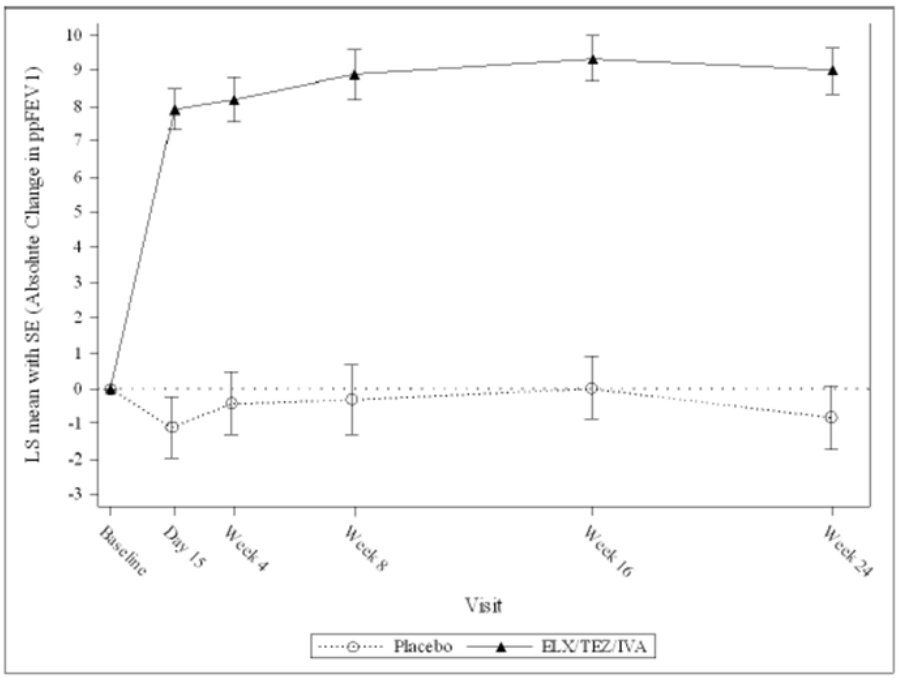
The efficacy analyses of Study 124 (n = 307) were performed on the Full Analysis Set (FAS): all randomised subjects who carry any intended mutation and received at least 1 dose of study drug.

Outcomes and estimation

Primary endpoint: ppFEV1

Treatment with ELX/TEZ/IVA resulted in a statistically significant improvement in absolute change from baseline in ppFEV1 through Week 24 compared to placebo, with least squares (LS) mean treatment difference of 9.2 percentage points (95% CI: 7.2, 11.3, *P* <0.0001). MMRM analysis of absolute change from baseline in ppFEV1 at each visit is shown in **Figure *10***. Descriptive statistics (mean [SD]) of the ppFEV1 values are shown in **Table *8*** for the purpose of comparison with the outcomes of the subgroup analyses.

Figure 10: MMRM analysis of absolute change from baseline in ppFEV1 (percentage points) at each visit up to Week 24 (FAS)



Source: Module 2.7.3/Figure 4
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effect model of repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RF: residual function; TEZ: tezacaftor
Notes: Baseline is defined as described in Module 2.7.3/Section 1.3.1.6. MMRM included data from all available visits up to Week 24, with treatment, visit, and treatment-by-visit as fixed effects and baseline $ppFEV_1$, age at screening (<18 vs ≥18 years), and mutation group (contains ≥1 RF-like mutation versus does not contain

Table 8: Summary of ppFEV1 (%) and change from baseline at each visit up to Week 24 (FAS)

Visit	Statistics	Placebo N = 102	ELX/TEZ/IVA N = 205
Baseline	n	102	205
ppFEV1	Mean (SD)	68.1 (18.1)	67.5 (17.6)
Day 15	n	82	169
ppFEV1	Mean (SD)	65.0 (18.4)	74.1 (17.4)
Absolute change from baseline	Mean (SD)	-1.8 (6.5)	7.9 (9.2)
Week 4	n	85	166
ppFEV1	Mean (SD)	65.9 (17.9)	73.2 (17.7)
Absolute change from baseline	Mean (SD)	-0.8 (7.7)	8.0 (9.5)
Week 8	n	88	170
ppFEV1	Mean (SD)	66.1 (18.9)	74.2 (17.6)
Absolute change from baseline	Mean (SD)	0.0 (7.9)	8.5 (10.1)
Week 16	n	89	168
ppFEV1	Mean (SD)	66.4 (18.6)	74.5 (18.0)
Absolute change from baseline	Mean (SD)	-0.3 (7.1)	9.3 (9.3)
Week 24	n	91	160
ppFEV1	Mean (SD)	66.1 (18.8)	74.6 (18.4)
Absolute change from baseline	Mean (SD)	-0.9 (7.7)	9.5 (9.8)

Secondary endpoints: SwCl, CFQ-R RD, Weight, BMI, PEx

Treatment with ELX/TEZ/IVA resulted in a statistically significant improvement (i.e. reduction) in absolute change from baseline in SwCl through Week 24 compared to placebo, with an LS mean treatment difference of -28.3 mmol/L (95% CI: -32.1, -24.5 mmol/L, *P* <0.0001).

Treatment with ELX/TEZ/IVA resulted in a statistically significant improvement in CFQ-R RD score through Week 24 compared to placebo, with an LS mean treatment difference of 19.5 points (95% CI: 15.5, 23.5, *P* <0.0001) (**Table *9*Table *9***).

Treatment with ELX/TEZ/IVA resulted in a statistically significant increase in Weight through Week 24 compared to placebo, with an LS mean treatment difference of 1.3 kg (95% CI: 0.6, 1.9, *P* <0.0001) and an increase in weight-for-age z-score of 0.06 (95% CI: -0.06, 0.18) for subjects ≤20 years of age (**Table *9***).

Treatment with ELX/TEZ/IVA resulted in a statistically significant increase in BMI through Week 24 compared to placebo, with an LS mean treatment difference of 0.47 kg/m2 (95% CI: 0.24, 0.69, *P* <0.0001) and an increase in BMI-for-age z-score of 0.08 (95% CI: -0.06, 0.22) for subjects ≤20 years of age (**Table *9***).

Treatment with ELX/TEZ/IVA resulted in a statistically significant reduction in PEx through Week 24, with a PEx rate that was 72% lower in the ELX/TEZ/IVA group than the placebo group (rate ratio = 0.28; 95% CI: 0.15, 0.51; *P* <0.0001). The annual event rate was 0.17 in the ELX/TEZ/IVA group versus 0.63 in the placebo group (**Table 9**).

Sensitivity analysis

The result of the sensitivity analysis, an MMRM based on multiple imputations, was consistent with the primary analysis.

Table 9: Study 124 primary and secondary efficacy analyses (FAS)

Analysis	Statistic	Placebo N = 102	ELX/TEZ/IVA N = 205
Primary Endpoint			
Absolute change from baseline in $ppFEV_1$ through Week 24 (percentage points)	n	98	192
	LS mean (SE)	-0.4 (0.8)	8.9 (0.6)
	95% CI of LS mean	(-2.0, 1.3)	(7.7, 10.0)
	LS mean difference, 95% CI	--	9.2 (7.2, 11.3)
	P value versus placebo	--	<0.0001
Secondary Endpoints			
Absolute change from baseline in SwCl through Week 24 (mmol/L)	n	100	200
	LS mean (SE)	0.5 (1.6)	-27.8 (1.1)
	95% CI of LS mean	(-2.6, 3.6)	(-30.0, -25.6)
	LS mean difference, 95% CI	--	-28.3 (-32.1, -24.5)
	P value versus placebo	--	<0.0001
Absolute change from baseline in CFQ-R RD through Week 24 (points)	n	102	202
	LS mean (SE)	-2.0 (1.6)	17.5 (1.2)
	95% CI of LS mean	(-5.2, 1.3)	(15.2, 19.8)
	LS mean difference, 95% CI	--	19.5 (15.5, 23.5)
	P value versus placebo	--	<0.0001
Absolute change from baseline in BMI at Week 24 (kg/m^2)	N	102	196
	LS mean (SE)	0.35 (0.09)	0.81 (0.07)
	95% CI of LS mean	(0.16, 0.53)	(0.68, 0.94)
	LS mean difference, 95% CI	--	0.47 (0.24, 0.69)
	P value versus placebo	--	<0.0001
Absolute change from baseline in weight at Week 24 (kg)	n	102	196
	LS mean (SE)	1.2 (0.3)	2.4 (0.2)
	95% CI of LS mean	(0.6, 1.7)	(2.1, 2.8)
	LS mean difference, 95% CI	--	1.3 (0.6, 1.9)
	P value versus placebo	--	<0.0001
Number of PEx through Week 24	Number of subjects with events, n (%)	26 (25.5)	18 (8.8)
	Number of events	40	21
	Estimated event rate per year	0.63	0.17
	Rate ratio, 95% CI	--	0.28 (0.15, 0.51)
	P value versus placebo	--	<0.0001

Source: Module 2.7.3/Table 9

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; ELX: elexacaftor; FAS: Full Analysis Set; IV: intravenous; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

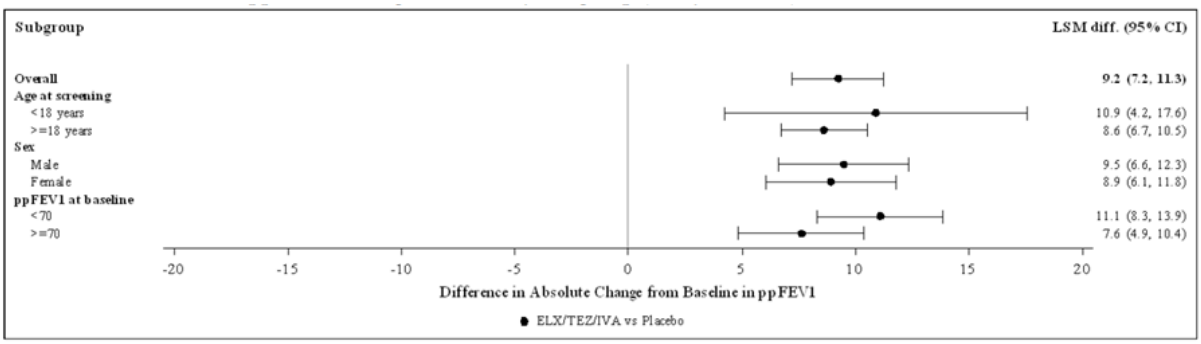
Notes: Definition of baseline and analysis approaches are described in Module 2.7.3/Section 1.3.1.6.

Ancillary analyses

Subgroup analyses

Prespecified subgroup analyses of the primary endpoint were performed for age (<18 years versus ≥18 years), baseline ppFEV1 (<70 versus ≥70) and sex (male versus female) in a manner similar to the primary analysis. Results are shown in **Figure *11*** and were generally consistent with the primary analysis, i.e. regardless of age, baseline ppFEV1, or sex, ELX/TEZ/IVA treatment resulted in improvements in the primary endpoint.

Figure 11: Study 124 Forest plot of LS mean difference between treatments with 95% CI for absolute change from baseline in ppFEV1 through Week 24 by subgroup (FAS)



Source: Study 124 CSR/Figure 14.2.1.2
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LSM: least squares mean; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Discriminatory value of the FRT test

Post-hoc, the discriminatory statistics of the FRT Assay was tested for those E/T/I FRT tested CFTR variants with available clinical trial data for ≥ 5 patients.

The threshold for ppFEV1 was a mean increase from baseline of ≥ 0% pp, and for SwCl a mean decrease from baseline of ≥ 10 mmol/L.

The provided discriminatory statistics are provided in **Table *10***

Table 10: Discriminatory statistics for FRT (10% threshold) predictive value for clinical benefit of E/T/I

	increase from baseline in ppFEV1 ≥ 0%	***decrease from baseline SwCl ≥ 10 mmol/L***
Sensitivity	10/11 (90%)	8/9 (89%
Specificity	Cannot be calculated	1/1 (100%
Positive predictive value	10/10 (100%)	1/2 (50%
Negative predictive value	0/1 (100%)	1/1 (100%)

CFTR mutations showing a ≥ 0% increase from baseline in ppFEV1 are F508del and from study 124 G85E, D1152H, R347P, L206W, A455E, M1101K, R1066H, R347H, L1077P. This is supported with the F508del mutation of study 102. The N1303K has no in vitro response but has a clinical response.
CFTR mutations showing a ≥ 10 mmol/l decrease in SwCl are F508del, G85E, R347P, L206W, A455E, M1101K, R1066H, R347H, but not D1552H The N1303K has both no in vitro response, and no clinical response.

Paediatric population (patients aged 6-12 years)

A total of 31 patients (10%) aged 6-12 years were included. A total of 23 were randomised to E/T/I and a total of 8 were randomised to placebo.

Table *11* Provides the average change from baseline in the primary and secondary outcomes for the 23 patients randomised to E/T/I. Overall these outcomes align with the data reported in the clinical studies.

Table 11: Summary of Average Change from Baseline in Primary and Secondary Efficacy Endpoints Through Week 24 for Subjects 6 Through 11 Years of Age, Study 124 FAS

		ELX/TEZ/IVA N = 23				
Visit	Statistics	ppFEV$_1$ (%)	SwCl (mmol/L)	CFQ-R RD Score (points)	BMI (kg/m^2)	Weight (kg)
Baseline	n	23	23	23	23	23
	Mean (SD)	79.4 (12.6)	95.5 (17.4)	77.5 (15.8)	16.29 (2.05)	30.0 (7.8)
Average through Week 24	n	19	23	23	22	22
	Mean (SD)	89.0 (14.6)	57.8 (21.3)	86.3 (12.8)	17.12 (2.63)	33.1 (8.9)
Average change through Week 24[a]	n	19	23	23	22	22
	Mean (SD)	10.2 (16.1)	-37.7 (18.8)	8.8 (16.2)	0.75 (0.87)[a]	2.6 (2.1)[a]

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. For SwCl and ppFEV$_1$, measurements at Day 15 were not included in the calculation for the average change from baseline through Week 24.

[a] BMI and weight results are absolute change at Week 24.

FRT-responsive and splice mutation subgroup analysis

ppFEV1, SwCl and CFQ-R RD score were analysed separately for subjects with FRT-responsive CFTR mutations and those with non-canonical splice mutations (*2789+5G>A*, *3272-26A>G*, *3849+10kbC>T*). For each of the mutations (see

Table ***5***) at least 1 subject was enrolled in Study 124.

Improvements in ppFEV1 and CFQ-R RD were comparable between the two subgroups. Mean (SD) change from baseline through Week 24 in ppFEV1 was 8.7 (10.3) percentage points in the FRT-responsive mutation subgroup (N = 129) and 8.9 (8.8) percentage points in the splice mutation subgroup (N = 82). Mean (SD) change from baseline through Week 24 in CFQ-R RD score was 17.4 (19.0) points in the FRT-responsive mutation subgroup and 17.7 (19.3) points in the splice mutation subgroup.

For SwCl, a difference was observed between the two subgroups. Mean (SD) change from baseline through Week 24 in SwCl was -35.4 (20.4) mmol/L in the FRT-responsive mutation subgroup, whereas it was -15.4 (10.4) mmol/L in the splice mutation subgroup. Baseline values were comparable with 78.1 (28.1) mmol/L and 79.3 (26.4) mmol/L, respectively.

Ad Hoc By-CFTR-mutation analysis

PpFEV1, SwCl and CFQ-R RD score were analysed by CFTR mutation for subjects in the ELX/TEZ/IVA group. Only CFTR mutations were included if ≥5 subjects had evaluable data, which was the case for 12 mutations (9 FRT-responsive mutations and 3 splice mutations). The results are presented as an improvement within the specific subgroup and no comparison with placebo was made.

The results were generally consistent with the overall ELX/TEZ/IVA group (ppFEV1 +9.5 [9.8] percentage point, SwCl -29.6 [21.4] mmol/L, CFQ-R RD +19.7 [20.7] points), although absolute changes from baseline varied substantially between mutations for all three parameters (Table 12). Mean (SD) absolute change from baseline in ppFEV1 through Week 24 ranged from 3.4 (5.1) percentage points to 17.3 (10.0) percentage points. Mean (SD) absolute change from baseline in SwCl through Week 24 ranged from -9.3 (7.3) mmol/L to -59.2 (14.6) mmol/L. Mean (SD) absolute change from baseline in CFQ-R RD score through Week 24 ranged from 8.1 (23.2) points to 31.4 (17.8) points.

Table 12: Study 124 By-mutation analysis: summary of absolute change from baseline in ppFEV1, SwCl and CFQ-R RD score by CFTR mutation at Week 24 (FAS)

	ELX/TEZ/IVA N = 205		
Genotype Statistic	ppFEV$_1$ (percentage points)	SwCl (mmol/L)	CFQ-R RD (points)
3849+10kbC>T			
n	30	30	30
Mean (SD)	11.6 (8.8)	-16.4 (9.6)	17.7 (19.4)
G85E			
n	29	33	32
Mean (SD)	12.4 (11.9)	-37.3 (17.6)	23.4 (20.2)
2789+5G>A			
n	26	25	26
Mean (SD)	5.8 (7.9)	-16.4 (13.3)	17.5 (18.7)
3272-26A>G			
n	23	25	25
Mean (SD)	8.8 (8.9)	-13.1 (7.8)	18.1 (20.6)
D1152H			
n	18	18	19
Mean (SD)	3.4 (5.1)	-9.3 (7.3)	12.7 (18.8)
R347P			
n	17	18	18
Mean (SD)	9.8 (9.9)	-38.5 (15.2)	13.6 (17.9)
L206W			
n	13	15	14
Mean (SD)	3.9 (5.6)	-43.5 (18.0)	11.7 (18.9)
A455E			
n	12	14	14
Mean (SD)	8.6 (9.2)	-33.3 (11.2)	19.5 (15.7)
M1101K			
n	8	8	8
Mean (SD)	12.0 (9.5)	-49.2 (19.0)	31.4 (17.8)
R1066H			
n	6	6	6
Mean (SD)	4.6 (7.4)	-59.2 (14.6)	10.4 (13.8)
R347H			
n	5	5	5
Mean (SD)	5.7 (6.1)	-21.3 (4.5)	8.1 (23.2)
L1077P			
n	5	<5	<5
Mean (SD)	17.3 (10.0)	--	--

Source: Module 2.7.3/Table 17
CFQ-R RD: Cystic Fibrosis Questionnaire – Revised Respiratory Domain; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: number of subjects with non-missing parameter for the corresponding mutation; N: total sample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor
Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period Subjects with 2 eligible *CFTR* mutations were included in the analysis for both mutations. SwCl and CFQ-R RD results are not presented for *L1077P* because there were <5 subjects with evaluable data.

Source: Module 2.7.3/Table 17
CFQ-R RD: Cystic Fibrosis Questionnaire – Revised Respiratory Domain; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: number of subjects with non-missing parameter for the corresponding mutation; N: total sample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor
Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period Subjects with 2 eligible *CFTR* mutations were included in the analysis for both mutations. SwCl and CFQ-R RD results are not presented for *L1077P* because there were <5 subjects with evaluable data.

Table 13 Ad hoc table for the CFTR mutations with subjects < 4 mutations

	ELX/TEZ/IVA		
Genotype statistic	**ppFEV1 (percentage points**	**SwCl (mmol/L)**	**CFQ-R-RD (points**
L1077F			
N	5	4	4
Mean (SD)	17.3 (10.0)	-40.15 (28.49)	23.6 (8.0)

L997F			
n	4	4	4
Mean (SD)	6.2 (8.88)	-11.25 (29.01)	5.67 (10.57)
P5L			
n	4	4	4
Mean (SD)	-6.8 (5.25)	-33.03 (20.97)	-9.025 (22.53)
R117C			
n	2	2	2
Mean (SD)	8.95 (1.48)	-35.95 (14.91)	26.75 (5.44)
S945L			
N	3	2	3
Mean (SD)	12.23 (14.10)	-49.8 (21.21)	28.7 (31.7)
V232D			
n	4	4	4
Mean (SD)	12.42 (19.3)	-72.45 (10.59)	6.4 (22.25)

Δ = Absolute change from baseline through week 24.

Specific ad hoc subgroup of study 124 : those harbouring an N1303K mutation

The analyses of the included CFTR mutations revealed that a total of 20 patients of study VX124 harboured the applied N1303K mutation as a second allele.
Among the subjects with an N1303K mutation, the results aligned with the overall trial population with a mean (SD) average change from baseline through Week 24; i.e., ppFEV1: 13.4 (12.6) percentage points, SwCl: -27.3 (16.8) mmol/L, and CFQ-R RD: 15.9 (19.5) points.

Summary of main studies

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

Table 14: Summary of Efficacy for trial VX21-445-124

Title: A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-*F508del* ELX/TEZ/IVA-responsive *CFTR* Mutation		
Study identifier	EudraCT Number: 2021-005320-38	
Design	Randomised, placebo-controlled, double-blind, parallel group, multicentre, ≥6 years of age, CF, ≥1 qualifying ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutation and no exclusionary mutation	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable for extension subjects enrolled in a follow-up study (VX21-445-125)
Hypothesis	Superiority	
Treatments groups	ELX/TEZ/IVA	200mg elexacaftor qd / 100mg tezacaftor qd / 150mg ivacaftor q12h for 24 weeks, or 100mg ELX qd / 50mg TEZ qd / 75mg IVA q12h for 24 weeks for subjects <12 years and <30 kg N = 205 (randomised)
	Placebo	0mg elexacaftor qd / 0mg tezacaftor qd / 0mg ivacaftor q12h for 24 weeks N = 102 (randomised)

Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change in ppFEV1 from baseline through Week 24
	Secondary endpoint	SwCl	Absolute change in SwCl from baseline through Week 24
	Secondary endpoint	CFQ-R RD	Absolute change in CFQ-R RD score from baseline through Week 24
	Secondary endpoint	PEx	Number of pulmonary exacerbations through Week 24
	Secondary endpoint	BMI	Absolute change in BMI from baseline at Week 24
	Secondary endpoint	Weight	Absolute change in Weight from baseline at Week 24
	Other endpoint	BMI z-score	Absolute change in BMI z-score from baseline at Week 24 for subjects ≤20 years of age
	Other endpoint	Weight z-score	Absolute change in Weight z-score from baseline at Week 24 for subjects ≤20 years of age
Database lock	05 July 2023 (date last subject completed the last visit)		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full Analysis Set (FAS): all randomised subjects who carry any intended mutation and received at least 1 dose of study drug – 24 weeks		

Descriptive statistics and estimate variability	Treatment group	ELX/TEZ/IVA	placebo
	Number of subjects	205	102
	LS mean ppFEV1 (through week 24)	8.9	-0.4
	95% CI of LS mean	7.7, 10.0	-2.0, 1.3
	LS mean SwCl (through week 24)	-27.8	0.5
	95% CI of LS mean	-30.0, -25.6	-2.6, 3.6
	LS mean CFQ-R RD (through week 24)	17.5	-2.0
	95% CI of LS mean	15.2, 19.8	-5.2, 1.3
	Number of PEx (through week 24)	21	40
	Estimated event rate per year	0.17	0.63
	LS mean BMI (at week 24)	0.81	0.35

	95% CI of LS mean	0.68, 0.94	0.16, 0.53
	LS mean Weight (at week 24)	2.4	1.2
	95% CI of LS mean	2.1, 2.8	0.6, 1.7
	Number of subjects ≤20 years of age	52	26
	LS mean BMI z-score (at week 24)	0.22	0.14
	95% CI of LS mean	0.14, 0.30	0.03, 0.25
	LS mean Weight z-score (at week 24)	0.21	0.14
	95% CI of LS mean	0.14, 0.27	0.05, 0.24

Effect estimate per comparison	Primary endpoint	Comparison groups	ELX/TEZ/IVA vs placebo
		LS mean ppFEV1	9.2
		95% CI	7.2, 11.3
		P-value	<0.0001
	Secondary endpoint	Comparison groups	ELX/TEZ/IVA vs placebo
		LS mean SwCl	-28.3
		95% CI	-32.1, -24.5
		P-value	<0.0001
	Secondary endpoint	Comparison groups	ELX/TEZ/IVA vs placebo
		LS mean CFQ-R RD	19.5
		95% CI	15.5, 23.5
		P-value	<0.0001
	Secondary endpoint	Comparison groups	ELX/TEZ/IVA vs placebo
		PEx rate ratio	0.28
		95% CI	0.15, 0.51
		P-value	<0.0001
	Secondary endpoint	Comparison groups	ELX/TEZ/IVA vs placebo
		LS mean BMI	0.47
		95% CI	0.24, 0.69
		P-value	<0.0001
	Secondary endpoint	Comparison groups	ELX/TEZ/IVA vs placebo
		LS mean Weight	1.3
		95% CI	0.6, 1.9
		P-value	<0.0001

	Other endpoint	Comparison groups	ELX/TEZ/IVA vs placebo Subjects ≤20 years
		LS mean BMI z-score	0.08
		95% CI	-0.06, 0.22
		P-value	0.2451
	Other endpoint	Comparison groups	ELX/TEZ/IVA vs placebo Subjects ≤20 years
		LS mean Weight z-score	0.06
		95% CI	-0.06, 0.18
		P-value	0.3080
Notes	N/A		
Analysis description	**Subgroup analysis** Subgroup analyses of the primary endpoint were performed for age (<18 years versus ≥18 years), baseline ppFEV1 (<70 versus ≥70) and sex (male versus female) in a manner similar to the primary analysis. Results were generally consistent with the primary analysis, i.e. regardless of age, baseline ppFEV1, or sex, ELX/TEZ/IVA treatment resulted in improvements in the primary endpoint. **FRT-responsive and splice mutation subgroup analysis** ppFEV1, SwCl and CFQ-R RD score were analysed separately for subjects with FRT-responsive CFTR mutations and those with non-canonical splice mutations. Improvements in ppFEV1 and CFQ-R RD were comparable between the two subgroups. For SwCl, a difference was observed between the two subgroups through Week 24, while baseline values were comparable. **Ad Hoc By-CFTR-mutation analysis** ppFEV1, SwCl and CFQ-R RD score were analysed by CFTR mutation for subjects in the ELX/TEZ/IVA group (if n ≥ 5). 12 mutations were included in the analysis. The results were generally consistent with the overall ELX/TEZ/IVA group, although absolute changes from baseline for all three parameters varied substantially between mutations.		

Clinical studies in special populations

Study 124 included children ≥6 years, adolescents and adults, including patients aged ≥65 years.

Subgroup analyses of the primary endpoint were performed for age (<18 years versus ≥18 years), baseline ppFEV1 (<70% versus ≥70%) and sex (male versus female) in a manner similar to the primary analysis. Results were generally consistent with the primary analysis, i.e. regardless of age, baseline ppFEV1, or sex, ELX/TEZ/IVA treatment resulted in improvements in the primary endpoint (**Figure *11***).

For patients ≤20 years of age, Weight-for-age z-score and BMI-for-age z-score remained stable.

Supportive studies

VX21-445-125: a Phase 3, multicentre, open-label extension study to Study 124

Study 125 is an ongoing Phase 3, multicentre, open-label study for subjects who completed the last Treatment Period visit of parent Study 124 and met the eligibility criteria. The study has a 96-week Treatment Period.

This submission includes efficacy results from a data cut occurring after all subjects had completed their Week 4 Visit (cut-off date: 28 August 2023). Only data up until the Week 4 Visit were included in the analysis. At this timepoint, subjects who received placebo in the parent study had been treated with ELX/TEZ/IVA for a total of 4 weeks and subjects who received ELX/TEZ/IVA in the parent study had been treated with ELX/TEZ/IVA for a total of 28 weeks. For subjects ≥6 and <12 years, dose was adjusted upwards where needed as subjects increased in age and weight.

Endpoints and endpoint analysis

The study's primary endpoint is safety. Secondary efficacy endpoints evaluated at the Week 4 data cut were absolute changes from baseline through Week 4 in ppFEV1, SwCl and CFQ-R RD score. An MMRM approach similar to Study 124 was used for all secondary endpoints.

Subgroup analyses – Ad Hoc By-CFTR-mutation analysis

Subgroup analyses were performed for all secondary endpoints (ppFEV1, SwCl and CFQ-R RD score):

- By-mutation analyses for each CFTR mutation that had at least 5 subjects with evaluable data (irrespective of their treatment in the parent study).

Results

Of the 298 subjects who completed drug treatment in the parent study, 297 subjects were enrolled in Study 125, including 195 from the parent study ELX/TEZ/IVA group and 102 subjects from the parent study placebo group. No subjects had prematurely discontinued treatment by the Week 4 data cut. Demographics and baseline (i.e. the most recent measurement before the first dose in the parent study) characteristics were generally similar to the parent study (see **Table *6*** and **Table *7***).

The efficacy analyses at Week 4 data cut of Study 125 (n = 297) were performed on the Open-label Full Analysis Set (OL-FAS): all enrolled subjects who received at least 1 dose of study drug in the open-label study. Results are shown in Table 15.

For subjects who received ELX/TEZ/IVA in the parent study, the improvements in ppFEV1, SwCl and CFQ-R RD were generally maintained for the first 4 weeks of ELX/TEZ/IVA treatment in Study 125.

For subjects who received placebo in the parent study, similar improvements in ppFEV1, SwCl and CFQ-R RD were observed following ELX/TEZ/IVA treatment initiation in Study 125. In Study 124, the mean (SD) change from baseline at Week 4 was 8.0 (9.5) percentage points in the ELX/TEZ/IVA group, comparing to a mean (SD) change from baseline at Week 4 of 7.1 (7.3) percentage points for subjects who initiated ELX/TEZ/IVA treatment in Study 125.

Table 15: Summary of Study 125 efficacy results at OL Week 4 (OL-FAS)

	Placebo in Study 124 N = 102	ELX/TEZ/IVA in Study 124 N = 195
ppFEV$_1$ (percentage points)		
Parent study baseline		
n	102	195
Mean (SD)	68.1 (18.1)	67.3 (17.4)
Absolute change from baseline at Week 4		
n	86	170
Mean (SD)	7.1 (7.3)	10.1 (11.0)
SwCl (mmol/L)		
Parent Study Baseline		
n	100	192
Mean (SD)	75.2 (28.7)	79.9 (26.9)
Absolute change from baseline at Week 4		
n	99	182
Mean (SD)	-27.4 (18.9)	-30.3 (21.9)
CFQ-R RD (points)		
Parent Study Baseline		
n	102	192
Mean (SD)	65.8 (21.3)	64.0 (20.5)
Absolute change from baseline at Week 4		
n	102	188
Mean (SD)	14.7 (22.6)	20.1 (20.7)

Sources: Study 125 Week 4 Report/Ad hoc Table 4, Ad hoc Table 6, and Ad hoc Table 8

CFQ-R RD: Cystic Fibrosis Questionnaire – Revised Respiratory Domain; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open label; ppFEV$_1$; percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline is defined as described in Section 1.3.1.6. For CFQ-R, the Children Ages 6 to 11 Version, Children Ages 12 and 13 Version, and Adolescent and Adults Version were pooled for analysis

Ad Hoc By-CFTR-mutation analysis

By-mutation analyses were performed for 16 mutations (13 FRT-responsive mutations and 3 splice mutations). The results were generally consistent with the overall results (ppFEV1 +7.1 [7.3] percentage points and +10.1 [11.0] percentage points; SwCl –27.4 [18.9] mmol/L and –30.3 [21.9] mmol/L; CFQ-R RD +14.7 [22.6] points and +20.1 [20.7] points for subjects receiving placebo and those receiving ELX/TEZ/IVA in Study 124 respectively), although absolute changes from baseline for all three parameters varied substantially between mutations (**Table *16***).

Mean (SD) absolute change from baseline (parent study) in ppFEV1 at Week 4 ranged from 4.3 (6.9) percentage points to 13.3 (12.1) percentage points. Mean (SD) absolute change from baseline in SwCl at Week 4 ranged from -12.0 (8.4) mmol/L to -69.5 (13.4) mmol/L. Mean (SD) absolute change from baseline in CFQ-R RD score at Week 4 ranged from -2.2 (31.1) points to 26.9 (25.9) points.

Table 16: Study 125 By-mutation analysis: summary of absolute change from baseline in ppFEV1, SwCl and CFQ-R RD score by CFTR mutation at OL Week 4 (OL-FAS)

Genotype Statistic	Any ELX/TEZ/IVA ppFEV$_1$ (percentage points)	SwCl (mmol/L)	CFQ-R RD (points)
G85E			
n	39	37	40
Mean (SD)	12.4 (11.2)	-35.3 (18.2)	20.4 (21.0)
3272-26A>G			
n	36	40	41
Mean (SD)	7.1 (8.8)	-13.9 (8.6)	18.2 (26.5)
3849+10kbC>T			
n	35	40	41
Mean (SD)	10.8 (10.5)	-17.2 (10.0)	19.4 (20.1)
2789+5G>A			
n	26	28	29
Mean (SD)	8.5 (9.5)	-20.6 (14.5)	19.7 (17.1)
R347P			
n	24	27	28
Mean (SD)	11.2 (10.0)	-40.1 (18.7)	19.5 (23.6)
D1152H			
n	23	23	24
mean (SD)	5.0 (5.9)	-12.0 (8.4)	13.7 (21.5)
A455E			
n	17	22	23
Mean (SD)	8.7 (9.7)	-32.2 (13.0)	15.3 (23.4)
L206W			
n	14	19	18
Mean (SD)	8.0 (7.8)	-45.4 (23.2)	17.8 (20.2)
M1101K			
n	12	14	14
Mean (SD)	8.7 (11.9)	-50.8 (17.4)	22.8 (21.7)
R1066H			
n	10	10	10
Mean (SD)	4.3 (6.9)	-62.9 (17.2)	17.6 (22.4)
L1077P			
n	7	7	7
Mean (SD)	13.3 (12.1)	-36.2 (27.6)	13.5 (17.8)
L997F			
n	7	7	7
Mean (SD)	7.0 (6.5)	-13.6 (12.8)	8.7 (10.6)
V232D			
n	6	5	6
Mean (SD)	9.4 (21.4)	-69.5 (13.4)	17.1 (24.2)
S945L			
n	5	6	6
Mean (SD)	13.0 (15.5)	-46.6 (14.8)	26.9 (25.9)
P5L			
n	<5	5	5
Mean (SD)	--	-29.4 (22.9)	-2.2 (31.1)
R117C			
n	<5	5	5
Mean (SD)	--	-39.5 (14.8)	20.6 (14.6)

Source: Module 2.7.3/Table 18

CFQ-R RD: Cystic Fibrosis Questionnaire – Revised Respiratory Domain; ELX: elexacaftor; IVA: ivacaftor; n: number of subjects with non-missing parameter for the corresponding mutation; OL FAS: Open-label Full Analysis Set; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Parent study baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. Subjects with 2 eligible *CFTR* mutations were included in the analysis for both mutations. ppFEV$_1$ data are not presented for *P5L* and *R117C* because there were <5 subjects with evaluable data.

Table 17 Study 125 By-mutation analysis: summary of absolute change from baseline in ppFEV1, SwCl and CFQ-R RD score by CFTR mutation Open Label Week 4 by Qualifying Mutations with less than 5 Non missing Values in Any of The 3 Endpoints OL All Subjects Set

	ELX/TEZ/IVA		
Genotype statistic	**ppFEV1 (percentage points**	**SwCl (mmol/L)**	**CFQ-R-RD (points**
P5L			
N	4	4	4
Mean (SD)	-4.1 (6.43)	-29 (26.4)	9.7 (18.35)
R117C			
n	4	4	4
Mean (SD)	7.08 (5.38)	-39.88 (17.08)	25.68(10.47)
R347H			
n	4	4	4
Mean (SD)	5.8 (7.81)	-21.13 (3.71)	4.2 (35.23)
T3381			
n	1	1	1
Mean (SD)	2.1	-39	-38.9

VX22-CFD-016: a non-interventional real-world evidence (RWE) study evaluating clinical outcomes in people with CF with ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations using data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR)

Based on data from the US CFFPR, this non-interventional RWE study provides additional supportive data, including data for less common non-*F508del* CFTR mutations that were not feasible to enrol in a clinical study. In total, 82 mutations were represented. The duration of ELX/TEZ/IVA treatment varied by patient, depending on the date on which the subject initiated ELX/TEZ/IVA treatment (the index date). Patient accrual was done in the period 21 October 2019 through 01 December 2022. For all patients, data were evaluated from up to 2 years before the index date (pre-initiation period) and from the index date until 31 December 2022 (follow-up period), as available.

A cohort of **422** patients was selected based on the following eligibility criteria:

- CFTR genotype: at least 1 of 182 ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations (177 FRT-responsive mutations and 5 splice mutations predicted to be responsive to ELX/TEZ/IVA).
- Evidence of treatment initiation with ELX/TEZ/IVA during the patient accrual period.
- ppFEV1: at least 1 ppFEV1 measurement and a mean baseline ppFEV1 ≥30% and ≤100% in the 12 months before the index date.
- Age: ≥6 years of age.

Endpoints and endpoint analysis

The primary endpoint was change from baseline in ppFEV1. The baseline ppFEV1 value for each patient was defined as the average of all in-clinic measurements in 12 months immediately preceding the index date (baseline year). The post-baseline ppFEV1 value for each patient was defined as the average of all in-clinic ppFEV1 measurements in the 12 months after the index date, excluding measurements within the 4 weeks immediately after index date. Baseline value, post-baseline value and change from baseline are summarised using descriptive statistics.

Secondary endpoints were nutritional parameters (Weight, Weight z-score, BMI, BMI z-score) and PEx. For the nutritional parameters, the baseline value was the last available measurement within the baseline year. The post-baseline value was the last available measurement within 12 months after the index date, excluding measurements within 6 months immediately after index date. Baseline value, post-baseline value and change from baseline are summarised using descriptive statistics.

PEx was defined based on the record of IV antibiotic use at home or in the hospital. Exposure-adjusted PEx rates were calculated for the pre-initiation and follow-up periods by dividing the total number of events by the total exposure time from all eligible patients.

Subgroup analyses

Subgroup analyses were performed for the primary endpoint:

- Subjects who had used other CFTR modulators during the baseline period versus those who were CFTR-modulator naïve.
- By-mutation analyses for each CFTR mutation that had at least 5 subjects with evaluable data.

Results

Demographic and baseline characteristics for Study CFD-016 are shown in

Table *18*. In general, demographic and baseline characteristics were comparable with those of Study 124, with the exception of ppFEV1 that was slightly higher in Study CFD-016 (74.15 [18.82] percentage points) compared to Study 124 (67.7 [17.7] percentage points). 55.45% of the CFD-016 study population had used CFTR modulators before.

Study CFD-016 found a mean change from baseline in ppFEV1 through the follow-up period of 4.53 percentage points (95% CI: 3.50, 5.56). The improvement in ppFEV1 was lower in patients who had previously received CFTR modulator treatment (3.32 percentage points [95% CI: 2.06, 4.58]) than in patients who had not (6.11 percentage points [95% CI: 4.40, 7.81]).

The results of the by-mutation analysis (20 mutations, shown in **Table *19***) varied substantially between mutations, with an absolute change from baseline in ppFEV1 from -4.0 (7.6) percentage points for mutation *R74W* (n = 8) to 25.7 (19.8) percentage points for mutation *R1066H* (n = 6).

After ELX/TEZ/IVA treatment initiation, improvements in weight and BMI were observed with a mean change from baseline of 2.91 kg (95% CI: 2.24, 3.58) for weight and 0.65 kg/m2 (95% CI: 0.41, 0.89) for BMI. The rate of PEx declined by 53% (95% CI: 42, 62).

Table 18: Study CFD-016 demographics and baseline characteristics (All Subjects Set)

Demographics	Total N=422
Age at ELX/TEZ/IVA initiation (years)	
n	422
Mean (SD)	29.81 (18.45)
Min, Max	6.20, 84.39
Age category at ELX/TEZ/IVA initiation, n (%)	
≥ 6 to <12 years	66/422 (15.64)
≥ 12 to <18 years	82/422 (19.43)
≥ 18 years	274/422 (64.93)
Gender, n (%)	
Male	176/422 (41.71)
Female	246/422 (58.29)
Prior CFTR modulator treated, n (%)	
Missing	2/422 (0.47)
No	186/422 (44.08)
Yes	234/422 (55.45)
Exposure length distribution (years)	
n	422
Mean (SD)	1.27 (0.58)
Min, Max	0.02, 3.11
Weight (kg)	416
n	60.84 (21.15)
Mean (SD)	
Weight z-score (subjects ≤20 years old)	
n	169
Mean (SD)	0.16 (1.17)
BMI (kg/m^2)	
n	416
Mean (SD)	23.37 (5.91)
BMI z-score (subjects ≤20 years old)	
n	169
Mean (SD)	0.36 (1.09)
$ppFEV_1$	
n	422
Mean (SD)	74.15 (18.82)

Source: Study CFD-016 CSR/Table 2.0

BMI: body mass index; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline values were defined as described in Section 1.3.2.5. A subject was counted as a prior CFTRm-treated if IVA, LUM/IVA, or TEZ/IVA was used within the 12 months prior to ELX/TEZ/IVA initiation. Weight and BMI z-scores were calculated only for subjects ≤20 years of age at ELX/TEZ/IVA initiation.

Table 19: Study CFD-016 By-mutation analysis: summary of absolute change from baseline in ppFEV1 by CFTR mutation with ≥5 patients with evaluable data.

Parameter	Total N = 422
G551D	
n	58
Mean (SD)	4.7 (11.4)
R117H	
n	42
Mean (SD)	1.0 (5.1)
D1152H	
n	21
Mean (SD)	3.4 (8.8)
G85E	
n	20
Mean (SD)	7.9 (7.1)
3849 + 10kb C->T	
n	16
Mean (SD)	2.5 (6.4)
R347P	
n	14
Mean (SD)	7.7 (10.8)
R668C	
n	16
Mean (SD)	0.1 (3.6)
S549N	
n	14
Mean (SD)	6.1 (11.6)
M1101K	
n	16
Mean (SD)	11.3 (11.8)
G576A	
n	13
Mean (SD)	0.6 (3.6)
A445E	
n	11
Mean (SD)	7.8 (9.0)
S945L	
n	11
Mean (SD)	4.1 (5.7)
P67L	
n	10
Mean (SD)	3.5 (13.2)
L206W	
n	7
Mean (SD)	1.9 (5.0)
R74W	
n	8
Mean (SD)	-4.0 (7.6)
D1270N	
n	7
Mean (SD)	0.5 (7.7)
2789 + 5G->A	
n	7
Mean (SD)	3.6 (6.4)
R347H	
n	5
Mean (SD)	0.5 (4.1)
R1066H	
n	6
Mean (SD)	25.7 (19.8)
T1036N	
n	5
Mean (SD)	7.1 (10.5)

Source: Module 2.7.3/Table 19

$ppFEV_1$: percent predicted forced expiratory volume in 1 second

Notes: $ppFEV_1$ baseline was defined as the average of all in-clinic assessments during the 12 months prior to the index date. Post-baseline $ppFEV_1$ was defined as the average of all in-clinic assessments recorded within 12 months post-index date (excluding the $ppFEV_1$ assessments within the 4 weeks after index date).

Expanded French Compassionate program

The expanded French compassionate program for elexacaftor–tezacaftor–ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. Burgel et al.
Lancet Respir Med 2024; 12: 888–900. Published Online August 13, 2024 https://doi.org/10.1016/ S2213-2600(24)00208-X.

Title study
The expanded French compassionate program for elexacaftor–tezacaftor–ivacaftor use in people with cystic fibrosis without a F508del *CFTR* variant: a real-world study

Inclusion criteria

This study provides real world data obtained in the French compassionate program that proved expanded access to E/T/TI to 497 pwCF aged ≥ 6 years without a F508del variants excluding those with two variants previously characterised as not responsive.

Methods
This is a prospective observational study conducted between May 2022 and March 2024.

Non-F pwCF Participants at France's 47 cystic fibrosis centres were given a 4–6 week trial of elexacaftor–tezacaftor–ivacaftor and response was determined by a centralised committee based on a combination of outcomes (including clinical symptoms, weight, concomitant treatments, sweat chloride concentration (SwCl), ppFEV1, and CT findings). The assessment considered all clinical evidence without specific criteria or cutoff values.
Additional post-hoc analyses were conducted on aggregated data from responders and non-responders to determine the proportion of participants that had a decrease in sweat chloride concentration of at least 20 mmol/L or an increase in ppFEV1 of 5 or more percentage points or 10 or more percentage points.

Assessment of CFTR variant responsiveness

The committee also assessed the responsiveness of individual CFTR variants as was derived based on the obtained clinical data. CF is a recessive disease and therefore, an observed clinical response implies that a least one of the included variants contribute to the effect. Therefore, knowledge is required for the responsiveness of the other variant in trans. In responders, the variant responsiveness can only be derived when two copies of the same variant are available, or if the other variant in trans is a non-responsive variant. If no response is observed, both alleles can be considered as non-responsive.

The committee used 5 categories to characterize the responsiveness of a certain CFTR variant i.e.

- Responsive: ≥3 pwCF with clinical response
- Probably responsive: 1-2 pwCF with clinical response
- Probably non-responsive: 1-2 pwCF without clinical response
- Non-responsive: ≥3 pwCF without clinical response
- Inconclusive: without sufficient conclusive data

Results

A total of 516 non-F pwCF were identified to participate.

- A total of 37 were excluded because of the presence of two variants that were identified as not responsive.
- A total of 479 pwCF entered the study, of which 250 males (52%). Most patients were aged ≥ 12 years (81%), the mean (95% CI) ppFEV1 was 64 (42-86)% and the mean (95% CI) SwCl was 97 (79-107) mmol/L.

- **Efficacy results**

Of the 479 enrolled non-F pwCF, a total of 114 pwCF harboured one of the 177 approved FDA CFTR variants, while an additional 365 patients were enrolled without an FDA-approved variant.

The committee concluded that a total of 290/479 (61%) pwCF showed a clinically positive treatment response. Responses were seen in 109/114 (96%) of pwCF with an FDA-approved variant and 181/365 (50%) pwCF with a non-FDA-approved variant.

The overall improvement in ppFEV1 was 7.75%. The mean (95% CI) ppFEV1 was 1.6 (0.5-2.8) % in the 183 non-responders with no FDA-approved variant; 11.1 (8.4 - 13.7) % in the 81 pwCF with at least one FDA-approved variant; 13.2 (11.4 - 15.0) % in patients with no FDA approved variant; and 4.9 (2.0, 7.7) % in the 36 included patients that received ivacaftor before entering the study.

The observed improvement in mean (95% CI) SwCl was -1.8 (-3.9, 0.3) mmol/L for the 183 non-responders with no FDA-approved variant; -44.5 (-39.1, -49.8) mmol/L in the 81 pwCF with at least one FDA-approved variant; -20.5 (-17.2, - 23.8) mmol/L in patients with no FDA-approved variant.

Except for n=36 patients, most included pwCF did not receive another modulator (i.e. ivacaftor) therapy before entering the study. Among the modulator naïve pwCF, a higher proportion of pwCF with an FDA-approved CFTR variant showed a response in the SwCl (≥ 20 mmol/L) compared to the population with a non-approved variant (82% vs 42%). The observed proportion of responders in ppFEV1 ≥ 5% was comparable (69% vs 78%).

- **CFTR variant responsiveness**

A total of 251 individual CFTR variants were identified, including 42/177 FDA approved variants based on the FRT data provided by study P289. Study U032 identified an additional 15/337 CFTR variants with clinical data.

The committee reviewed the clinical responses to determine the E/T/I responsiveness of a single variant. For a total of 54 /261 (21%) sufficient clinical data was available to unequivocally designate the responsiveness of a specific CFTR variant; for 64/261 (25%) the data was insufficiently conclusive, while for a total of 143 (96+47) /261 (55%) variants only a preliminary conclusion could be made.

The following 68 FRT responsive mutations were harboured by at least one of the participants. **Table 20** shows their responsiveness to treatment as adjudicated by the centralised committee.

Table 20: CFTR variant responsiveness determine by the Centralised Committee

FRT responsiveness	Study	Responsive(n≥ 3)	Probably responsive (n= 1-2)	Probably non-responsive (n=1-2)	Non responsive n≥ 3)	Inconclusive
FRT positive	**P289**	D1152H; G1249R G551D; G85E L206W;R347P S549N; S945L S977F	A455E; D110H; E92K; F311L; G178R; G576A, R668C ; H1054D; I601F; P205S; R1066H; R117H; R347H; R74W,V201M,D12	I175V; M152V *H199R*		A46D;E60K G628R; G1061R H1085R; P5L L165S; L997F M1101K; S1251N S492F; R117C I506T

			70N ; R933G; S13F; S364P; S549R; V1153E; V232D			
	U032		D985Y; E1004V; F1078S; Q552P; R31C; T1057R; I618N	K464N		E292K,; S1235R, T1086I;D1145N
FRT non responsive	**P289**	N1303K; R334W R1066C	G149R; A561E	A559T; M1T	I507del	M1V
	U032		A1067D	I601T; L558S		
Total included		12	29	8	1	18

Complex alleles are underlined to improve readability. This table included FRT testing data from both study P0289 and study U032.

Based on these data, the discriminatory statistics of the FRT Assay were calculated under different assumptions (Table 21), i.e.:

i. only those CFTR variants were included with a certain positive or non-positive result, i.e. 13 CFTR variants.
ii. the data set was extended with those CFTR mutations showing a possible positive or negative result, i.e. 50 CFTR variants.
iii. when the inconclusive CFTR variants (n=18) would contribute to a positive clinical result
iv. when the inconclusive CFTR variants (n=18) would contribute to a negative clinical result

Overall, the FRT Assay showed high sensitivity (0.75-0.89) and positive predictive value (0.63-1) under the various assumptions (**Table 21**)

Table 21: The discriminatory statistic of the FRT Assayfor included CFTR variants in the FCUP under various assumptions

Response attribution	**CFTR (n)**	**Sens**	**Spec**	**PPV**	**NPV**
i. only certain (non) responses CFTR variants	13	0.75	1	1	0.25
ii possible (non) responsible CFTR variants	50	0.85	0.56	0.90	0.45
Inconclusive data is included					
iii inconclusive variants are considered responsive	68	0.88	0.56	0.93	0.5
iv inconclusive data are considered non-responsive	68	0.85	0.22	0.63	0.5

Sens = sensitivity. Spec = specificity PPV =s positive predive value NPV = negative predictive value

- **Additional inclusion of the variants R334W and R1066CC**

The applicant also proposes to include the CFTR mutations R334 and R1066C based on the responsiveness demonstrated in the French CUP. The observed improvements in SwCl and ppFEV1 obtained for these mutations are summarized in **Table 22**.

Table 22: The mean change (95% CI) in SwCl an ppFEV1 in pwCF harbouring a R334W or R1066C mutation

	Absolute mean (95%) change SwCl after E/T/I (mmol/L)	**Absolute mean change (95% CI) ppFEV1 after E/T/I**	**Proportion ≥ 5% increase FEV1**
R334W (n=14)	-17.3 (-23.4, -11.3)	11.4 (4.1, 18.6)	12 (86%)
R1066C (n=8)	-41.2 (-60.1, -22.3)	21.4 (10.1 to 32.7)	7 (88%)
N1303K	-12 (-16.9, -7.1)	15.1 (11.3 to 18.9)	48 (80%)

Note: N1303K is another CFTR mutation that does not show an in vitro response, but demonstrated improvement in ppFEV1 in various single arm trials as discussed in the overview

Investigator-initiated clinical studies of the *N1303K* mutation

In response to the 2nd request for supplementary information, the following data was provided to support the N1303K application despite the lack of in vitro-response in the FRT assay.

1. Burgel et al. 2024
2. Solomon et al. 2024
3. Canan et al 2024
4. Kaftrio post-authorization safety study (PASS): US CFFPR data
5. Post hoc data subgroup analyses of patients harbouring a N1303K mutation in study 124

1 Burgel et al. 2024: Burgel et al. compiled data from 35 patients with CF with at least one N1303K mutation and without an F508del mutation who received off-label ELX/TEZ/IVA. ELX/TEZ/IVA was associated with clinically significant improvement in all 35 patients, leading to the decision of continuing treatment.

Results
The Median [IQR] age at E/T/I initiation was 23 [15; 31] years (range, 8-62). At baseline Median [IQR] sweat chloride concentrations were 107.0 [99.5; 112.5] mmol/L (n=33; missing in 2 cases) and median ppFEV1 was 49.5 [38.3; 70.5] percentage points (n=34; missing in 1 patient).

Efficacy
The median (interquartile range [IQR]) increase in ppFEV1 was 17.0 percentage points (10.0 to 25.0 percentage points) in all people with CF (N1303K/any; n = 34; P<0.0001), corresponding to a mean increase of 18.5 percentage points (95% CI: 14.2, 22.9).

Sweat chloride concentrations saw an overall (N1303K/any) median [IQR] decrease of 9.0 [3.5; 21] mmol/l (n=33; P<0.001; missing in 2).

Subgroup analyses

Results were generally consistent across different genotype subgroups with median changes (IQR) from baseline in ppFEV1 as follows:

	N	Median change from baseline	IQR
N1303K/N1303K:			
ppFEV1 %	11	11.0	10.0, 23
SwCl (mmol/L)	9	10.0	4.5, 31
N1303K/stop codon			
ppFEV1 %	14	16.5	9.0, 23
SwCl (mmol/L)	14	6.5	2.8, 12.3
N1303K/other			
ppFEV1 %	9	21	12, 31
SwCl (mmol/L)	10	13.5	0.8, 22.0

2 Solomon et al. 2024: In addition, preprints from Solomon et al. have now been published. In this study, total of 20 subjects with at least one N1303K variant and not eligible to receive CFTR modulator therapy were enrolled and received ELX/TEZ/IVA treatment for 28 days.

At 28 days, the mean SwCl reduction was -1.1 mmol/L (95% CI: -5.3, 3.1; P = 0.61). Mean improvement from baseline in ppFEV1 at Day 28 was 9.5% (95% CI: 6.7, 12.3; P<0.001) with 15 of 20 subjects showing at least a 5% increase in ppFEV1.
Improvements were also observed in mean Cystic Fibrosis Questionnaire-Revised Respiratory Domain (CFQ-R RD) score (20.8 points [95% CI: 11.9, 29.8; P<0.001]), BMI (0.4 kg/m2 [95% CI: 0.2, 0.7; P = 0.002]), and weight (1.0 kg [95% CI: 0.4, 1.7; P = 0.002]).
AEs were consistent with the known safety profile of ELX/TEZ/IVA.

3 Canan et al. 2024: This paper included case reports of a total of 4 adult patients in Brazil with CF who are heterozygous for N1303K and a non-F508del allele. The study showed improvements after 12 weeks of ELX/TEZ/IVA treatment. Three months after initiating ELX/TEZ/IVA, all 4 patients reported subjective reduction in cough frequency and sputum production. In addition, there was significant improvement in lung function (range 5-13 ppFEV1), BMI, and quality of life as measured by CFQ-R.
In patients with N1303K/MF genotypes, BMI increased by 0.65 to 2.19 kg/m2, CFQ-R RD increased by 5.55 to 83.34 points, and ppFEV1 increased by 10 to 17 percentage points. There were small variations in SwCl (range 2-17 mmol/L) and no safety-related events.

4 Kaftrio PASS (Study 120, MEA 002.6):

The ongoing ELX/TEZ/IVA PASS is a large registry-based study of CFTR modulator use to date and includes data from the US CFFPR. As of the last interim analysis completed (December 2023), there were 23 patients with an N1303K mutation and a non-ELX/TEZ/IVA-responsive mutation on the second CFTR allele exposed to ELX/TEZ/IVA, including 2 N1303K homozygous patients.

In the first year of exposure, the mean ppFEV1 increase from baseline was 4.57 percentage points (95% CI: 0.94, 8.19). In the subgroup of 18 patients with baseline ppFEV1 <90, the mean ppFEV1 increase from baseline was 6.09 percentage points (95% CI: 1.97, 10.22) (**Table *23***).

Table 23: Study 120 (PASS): Summary of ppFEV1 for Patients Heterozygous for the N1303K Mutation and a Non-ELX/TEZ/IVA-responsive Mutation

Endpoint Parameter	*N1303K* Analysis Cohort (N = 23)	*N1303K* Analysis Cohort, Subgroup with Baseline $ppFEV_1$ <90 (N = 18)
Pre-treatment Year -1		
n (non-missing)	23	18
Mean (SD)	68.22 (25.81)	59.38 (21.69)
Year 1 Change From Baseline		
n (non-missing)	23	18
Mean (SD)	4.57 (8.38)	6.09 (8.30)

Source: Study 120/Ad hoc Table 3

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PASS: post-authorization safety study; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: The baseline value is the average of all in-clinic assessments during the baseline period which is defined as up to the 12 months immediately preceding initiation of ELX/TEZ/IVA, change from baseline is the difference between post-baseline (average of all in-clinic assessments obtained from 4 weeks to 12 months after ELX/TEZ/IVA initiation) and baseline values.

5. Subgroup analyses of study 124:

Subgroup analyses for the n=20 patients in study 124 harbouring a N1303K mutation are provided. In contrast to the referred studies by Salomon and Sadras, these patients harboured a second, responsive CFTR allele.

Table 24 Summary of Average Change from Baseline in ppFEV1, SwCl, and CFQ-R RD Score Through Week 24 for Subjects with an N1303K Mutation, Study 124 FAS

		$ppFEV_1$ (%)	SwCl (mmol/L)	CFQ-R RD Score
Visit	Statistics	ELX/TEZ/IVA N = 20	ELX/TEZ/IVA N = 20	ELX/TEZ/IVA N = 20
Baseline	n	20	20	20
	Mean (SD)	63.2 (16.8)	79.5 (24.4)	67.4 (24.4)
Average through Week 24	n	19	19	20
	Mean (SD)	76.6 (15.0)	50.8 (23.3)	83.3 (10.6)
Average change through Week 24	n	19	19	20
	Mean (SD)	13.4 (12.6)	-27.3 (16.8)	15.9 (19.5)

Source: Adhoc Tables 14.2.1.8, 14.2.2.6, and 14.2.3.5.1

Summary of clinical evidence for N1303K

Overall, improvements were observed in ppFEV1 after 4 to 8 weeks of treatment that were comparable to the improvements found in the Studies 124, 125 and CFD-016. Changes in SwCl appeared minimal.

Table 25: Summary of efficacy results from N1303K data

Source Description		Data summary
Burgel et al. 2024	Compilation of data from: 1. Burgel et al 2023 (French Compassionate Program; n = 8 patients) 2.Dreano et al. 2023 (French Compassionate Program; n = 2 additional patients)	**N = 35** *N1303K* patients with CF Following ELX/TEZ/IVA initiation, improvement observed in $ppFEV_1$ (+17%)[a] median change from baseline

	3.Sadras et al 2023 (prospective, open- label study); n = 8 patients) 4.Published case reports (n = 3 patients; of which, 2 subjects were previously reported from Graeber et al. and Huang et al.) 5.Unpublished data from the French Compassionate Program (n = 14) Results published in peer-reviewed journal (European Respiratory Journal)	N1303K/N1303K (n=11) ; ppFEV1 +11%, SwCl -10 mmol/L N1303K/Stop codon (n=14): ppFEV1 +16% SwCl -6.5 mmol/L N1303K any (n=9): ppFEV1 +21%, SwCl -13.5 mmol/L
Solomon et al. 2024	Manuscript preprints of data previously presented at 2023 NACFC Manuscript is under review as of submission date of these responses.	Data consistent with NACFC materials: **N = 20** *N1303K* patients with CF Following ELX/TEZ/IVA initiation, improvements observed in ppFEV1 (+9.5%), CFQ-R RD (+20.8 points), and weight (+1.0 kg)[a]
Canan et al. 2024	Case reports of clinical outcomes Results published in peer-reviewed journal (*Archivos de Bronconeumología)*.	**N = 4** *N1303K* patients with CF Following ELX/TEZ/IVA initiation, improvements observed in ppFEV1 (range: 10 to 17%), CFQ-R RD (range: 5.55 to 83.34 points), and BMI (range: 0.65 to 2.19 kg/m^2) SwCl range -2 to -17 mmol/L
Kaftrio PASS	Post-authorization observational cohort study; drug utilization patterns assessed using data from patients treated with ELX/TEZ/IVA as collected by US CFFPR Cumulative drug utilization data previously presented in PASS/IA3 report (Procedure EMEA/H/C/005269/MEA/002.6); *N1303K* ppFEV1 data were not previously provided.	**N = 23** *N1303K* patients with CF Following ELX/TEZ/IVA initiation, improvement observed in ppFEV1 (+6.09%)[a]
Ad-hoc Subgroup N1303K Study 124	Ad-hoc subgroup of patients harbouring N1303K, patients harbour second responsive mutation	N=20 Average change trough week 24 ; mean (SD): ppFEV1 13.4 (12.6) % SwCl -27.3 (16.8) mmol/L

BMI: body mass index; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; IA: interim analysis; LCI: lung clearance index; n: size of subsample; N: total sample size; NACFC: North American Cystic Fibrosis Conference; PASS: post-authorization safety study; pp: percentage points; ppFEV1: percent predicted forced expiratory volume in 1 second

[a] Mean change from baseline

[b] Median change from baseline

2.4.2. Discussion on clinical efficacy

The Applicant has initially submitted a request to extend the indication of ELX/TEZ/IVA in combination with IVA as follows:

Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene ***or a mutation in the CFTR gene that is responsive based on clinical and/or* in vitro *data*** *(see section 5.1).*

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

Kalydeco

… In a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children aged 2 years and older with cystic fibrosis (CF) who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene ***that is responsive based on clinical and/or in vitro data (see section 5.1).***

Kalydeco

… In a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) ***gene that is responsive based on clinical and/or in vitro data (see section 5.1).***

ELX/TEZ/IVA treatment in combination with IVA was initially developed and licenced for people with CF carrying the *F508del* mutation. In Europe, this mutation is found in 80% of CF patients. The non-F508del population covers up to 20% of the EU CF population.

Patients harbouring non-*F508del* mutations generally still rely on symptomatic treatment only. An unmet medical need remains for more effective treatment that targets the underlying cause of the disease for these patients, particularly for patients with MF mutations. MF mutations are mutations that can be categorised as mutation with a Class I to III CFTR defects, however, modulator therapy will not be effective in patients harbouring a Class I mutation.

The Applicant has identified a subset of ~520 non-*F508del* mutations as ELX/TEZ/IVA-responsive:

- For most mutations (514) identification was based on responsiveness measured with the *in vitro* FRT model (FRT-responsive mutations).
- For 5 so-called non-canonical splice mutations that produce reduced amounts of normal CFTR protein, it has been previously shown that these are responsive to IVA and TEZ/IVA in clinical studies, and it is therefore expected these are responsive to ELX/TEZ/IVA as well.
- For a total of 82 FRT-responsive and splice mutations, the Applicant further substantiates ELX/TEZ/IVA responsiveness with clinical (18 mutations) and observational study data (82 mutations) from study CFD-016 and bibliographical data from the FCUP.
- For the *N1303K* mutation (not FRT-responsive or a splice mutation) bibliographical data of ELX/TEZ/IVA responsiveness was provided by investigator-initiated studies.
- For a total 2 non-E/T/I responsive mutation (R334W and R1066C), the inclusion is supported with bibliographical clinical data from the expanded French Compassionate Use Program (FCUP).

The applied mutations are specified in SmPC section 5.1 to which reference is made in the indication.

Design and conduct of clinical studies

The Applicant has submitted two new clinical studies, one observational study, and bibliographical data:

- Study 124 was a Phase 3, randomised, double blind, placebo-controlled, parallel group trial in CF patients aged ≥6 years with ≥1 ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutation and no *F508del* mutation. In this study, 18 of the most common ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations were included (15 FRT-responsive and 3 non-canonical splice mutations).
- Study 125 is an ongoing open-label follow-up study for patients who completed treatment in Study 124. The study was designed to support long-term safety (up to 96 weeks). For the purpose of this submission, an interim analysis on efficacy was performed after 4 weeks of treatment (Week 4 data cut).

- Study CFD-016 was a non-interventional Registry study to evaluate clinical outcomes in people with CF with ≥1 ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations using data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR).
- Bibliographical data: Expanded French compassionate program was a non-interventional observational study providing real world data. The study provided expanded access to E/T/I to 479 pwCF aged ≥ 6 years without a F508del variant excluding those with two variants previously characterised as not responsive.

This bibliographical data to support the application for N1303K consists of investigator initiated single arm studies (no. 1-3) supported with the results of the Kaftrio post authorisation study (no. 4) and post hoc analyses of study 124 of those patients harbouring also an N1303K mutation (no. 5), i.e.

- 1) Burgel et al. 2024 (peer reviewed)
- 2) Solomon et al. 2024 (under peer review)
- 3) Canan et al 2024. (peer reviewed)
- 4) Kaftrio post-authorization safety study (PASS): US CFFPR data.
- 5) Ad-hoc analyses subgroup study 124 patients harbouring a N1303K mutation

Study 124

Study 124 is presented as the pivotal study for extending the indication of Kaftrio to include CF patients with non-*F508del*, ELX/TEZ/IVA responsive mutations.

Design

Study 124 was a randomised, double-blind, parallel-group, placebo-controlled trial. The design of Study 124 was largely comparable to the pivotal phase 3 RCT Study 102 in F/MF subjects: placebo-controlled, 24 weeks, same primary (ppFEV1) and secondary endpoints (SwCl, CFQ-R RD score, number of PEx, BMI, Weight), similar statistical analysis (MMRM). The selected dose corresponds to the posology that is approved for patients with the *F508del* mutation.

Comparator

The inclusion of a placebo arm in the study is acceptable since no active comparator is approved in patients who do not harbour an *F508del* mutation for all included mutations, although some uncertainties remain about the contribution of each compound to treatment. Previous studies in the F508del population showed a benefit over IVA (F508del/gating mutations, Study VX18-445-104), TEZ/IVA (F508del/residual mutations, study VX18-445-104) and over placebo (F508del/ minimal function mutations, Study VX17-445-102).

Duration

A treatment duration of 24 weeks is in line with the EMA guideline on CF (CHMP/EWP/9147/08) and with the treatment duration in pivotal study 102.

Inclusion and exclusion criteria

The in- and exclusion criteria were generally acceptable, however, some criteria required further clarification:

Lung function

The initial lung function was restricted to patients with ppFEV1 between 40 and 90%, but the range of qualifying ppFEV1 values was expanded to broaden the eligible population. Inclusion of subjects with ppFEV1 90–100% is acceptable, since the percentage of subjects with this higher lung function was

limited to max. 10% of the study population. However, this subgroup might be less sensitive to show improvements.

Age limit

A lower age limit of 6 years was used. This is acceptable, as ELX/TEZ/IVA is already indicated in children (with *F508del* mutation) and sufficient data are available on use in children. Moreover, children aged ≥6 years are able to perform reliable spirometry tests.

No subjects aged 2 to 5 years were included. Kaftrio is already indicated for patients aged 2 to 5 years harbouring the *F508del* mutation. The application in the age group of 2 to 5 years harbouring a non-*F508del* can be extrapolated from older subjects aged 6 to 12 years based on the comparable PK exposure and the common underlying disease process of dysfunctional CFTR protein.

Diagnosis of CF

The study protocol did not provide clear diagnostic criteria for the diagnosis of CF. The included patients should harbour at least an eligible E/T/I response CFTR mutations, while the diagnosis of CF was mainly based on the investigator's judgement. This was accepted assuming that most of the studies will be conducted in specialised centres, although a more extensive evaluation would have been strongly preferred (e.g. additional CFTR function testing in case the sweat chloride < 59 mmol/l).

Criteria for selecting CFTR mutations for study 124

The selection criterium for the 18 CFTR mutations was based on their prevalence in the regions study in which study 124 was conducted. Mutations with the relative highest prevalence were included to increase the likelihood of enrolling patients and to provide subgroup analyses of at least ≥ 5 patients.

Endpoints and statistical analyses

The primary endpoint (absolute change from baseline in ppFEV1 through Week 24) and secondary efficacy endpoints (SwCl, CFQ-R RD score, BMI, Weight, Number of PEx) are all accepted endpoints in clinical trials on CF, with FEV1 being the advocated primary endpoint in the EMA guideline on CF.

The primary and secondary endpoint analyses were performed using MMRM models for ppFEV1, SwCl, CFQ-R RD, BMI, Weight, and binomial regression model for PEx. These outcomes were analysed using a similar approach as the analyses performed in Study 102, with slight differences in dependent variables (Day 15 included, Week 16 excluded) and covariates (mutation group included, sex excluded) with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. Type I error was properly controlled through a hierarchical testing-procedure.

Study 125

The open-label extension study 125 provided additional supportive efficacy data of 4 weeks of treatment, including the efficacy data of the placebo patients that were switched to active treatment.

Study CFD-016

The non-interventional real-world data (RWD) study CFD-016 provided supportive, uncontrolled data of 422 non-*F508del* CF patients harbouring at least one ELX/TEZ/IVA-responsive mutation over a variable period, based on data from the US CFFPR.

The US CFFPR is a comprehensive patient registry with data from approximately 32,000 people with CF, representing between 81% and 84% of all people with CF in the US, collected from over 130 CFF-accredited care centres. This registry collects spirometry measurements (for ppFEV1) according to the American Thoracic Society [ATS]/European Respiratory Society [ERS] Guidelines. Since 2019, the average number of spirometry measurements reported per individual ranged from approximately 2.5 to

4.8, [CF foundation] which is consistent with the clinical care guidelines issued by the CFF that recommend 2 to 4 assessments per year.[11] In addition, the US CFFPR performs a robust query and quality control review process of collected data annually. In a data quality audit, the US CFFPR was reported to have high accuracy and completeness of critical data when compared to medical records.[12]

Bibliographical data

Expanded French Compassionate program

The bibliographical data from the expanded French Compassionate program provided prospective observational, non-interventional real-world data (RWD) for homozygous non-F pwCF. The study was open for FRT responsive variants as well those CFTR variants without FRT data. The FRT data was either not available yet or the CFTR variants could not be evaluated by the FRT assay. pwCF homozygous for known non-responsive mutations, e.g. class I mutations, were excluded.

As the study was open to all non-F pwCF, this study included the non-F CFTR variants that occur most frequently in France.

A central FCP committee determined the clinical responsiveness after a 4-6 week trial of E/T/I based on combination a combination of outcomes without a specific threshold.

The central committee also adjudicated the responsiveness of a specific CFTR variant. In their evaluation, they considered the presence of the potential responsiveness of the other mutation in trans. This method differs from the clinical evaluation of the RCT, where the CFTR variant responsiveness was determined by the mean ppFEV1 and SwCl obtained in subgroups with ≥ 5 pwCF.

The French Compassionate use programme (FCP) method of evaluation is considered more precise in determining the responsiveness of a specific variant.

Efficacy data and additional analyses

Study 124

In total 307 subjects participated in Study 124, of whom 205 received ELX/TEZ/IVA treatment and 102 received placebo. 9 (2.9%) subjects (all in the ELX/TEZ/IVA group) prematurely discontinued treatment, of whom 5 (1.6%) due to an AE.

Demographic and baseline characteristics were balanced between the two treatment groups. More subjects with ppFEV1 >90% were included than planned (11.4% whereas max. 10% was defined). This slight deviation is not considered to affect the analysis of the primary endpoint.

Subjects were stratified into two categories based on whether they had at least one RF-like mutation (73.3%) or no RF mutation (26.7%), indicating that most study participants had phenotype associated with a less severe clinical presentation of CF. When comparing the baseline characteristics of the subjects in Study 124 with those in Study 102 (MF mutations only), it is observed that baseline ppFEV1 and BMI were slightly higher (approx. 6 percentage points and 1 kg/m^2 difference respectively), whereas baseline

[11] Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care: consensus conference report. Chest. 2004;125(1 Suppl):1S-39S.

[12] Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, et al. The Cystic Fibrosis Foundation patient registry: design and methods of a national observational disease registry. Ann Am Thorac Soc. 2016;13(7):1173-9.

SwCl was substantially lower in Study 124 (approx. 25 mmol/L difference), confirming a less severe clinical picture.

Endpoints

The study met its primary endpoint, and the additional secondary endpoints provided support for the efficacy.

For the primary endpoint, the LS mean treatment difference in absolute change in ppFEV1 through Week 24 between the ELX/TEZ/IVA and placebo groups was 9.2 percentage points (95% CI: 7.2, 11.3; $P < 0.0001$). Albeit lower than the LS mean treatment difference found in pivotal Study 102 in subjects with the *F508del* mutation (14.3 percentage points [95% CI: 12.7, 15.8]), this difference is still considered clinically relevant according to the Report of the workshop on endpoints for cystic fibrosis clinical trials (EMA/769571/2012).

For all secondary endpoints, significant and clinically improvements were found after 24 Weeks of treatment compared to placebo. The cross-study comparison with Study 102 show that the overall effects are somewhat smaller than observed in the subjects carrying the *F508del* mutation but still can regarded as relevant.

Subgroup analyses

Consistent and significant improvements in ppFEV1 favouring ELX/TEZ/IVA compared with placebo were observed across all prespecified subgroups (age, sex, ppFEV1 at baseline). In subjects <18 years, a substantially wider 95% CI was observed. This can be explained by a smaller number of subjects in this subgroup (approx. 25% of the study population, whereas the division based on sex and ppFEV1 at baseline was close to 50:50).

Subgroup analyses of the FRT-responsive mutations and the splice mutations showed comparable improvements in ppFEV1 and CFQ-R RD score. On the contrary, a marked difference in SwCl response was found. Mean (SD) change from baseline through Week 24 in SwCl was -35.4 (20.4) mmol/L in the FRT-responsive mutation subgroup, whereas it was -15.4 (10.4) mmol/L in the splice mutation subgroup. Baseline values were comparable with 78.1 (28.1) mmol/L and 79.3 (26.4) mmol/L, respectively.

Subgroup analysis revealed that some subjects harbour two of the included mutations. In case a subject has two CF-causing ELX/TEZ/IVA-responsive mutations, it cannot be discerned which of these two then facilitates the effect of the treatment.

In response to CHMP requests, the MAH provided an additional post hoc subgroup analysis of study 124 including subjects with only 1 qualifying mutation that are either (a) homozygous for the qualifying mutation or (b) have a mutation on the second allele that is predicted to make no CFTR protein (i.e., a nonsense mutation or a canonical splice mutation) showing comparable results with the overall population for improvement in ppFEV1 and SwCl. This subgroup analysis supported that the overall efficacy results of study 124 can be attributed to the responsive E/T/I CFTR mutation.

Study 125

A total of 297 out of 298 subjects who completed drug treatment in Study 124 were enrolled in Study 125 (195 ELX/TEZ/IVA-treated and 102 placebo-treated). Results of the efficacy analyses at Week 4 data cut were in line with the results from the parent study.

Study CFD-016

Registry data is only obtained in study CFD-016 using the US Cystic Fibrosis Registry for the FRT responsive mutations.

Study CFD provides supportive RWD data, including data for rare non-*F508del* CFTR mutations. 82 of the 182 eligible CFTR mutations were represented in the study cohort of 422 patients. The mean (SD) exposure length was 1.27 (0.58) years.

Since this study was non-interventional, it can be expected that any effects of ELX/TEZ/IVA treatment found in this study may be less pronounced due to various real-world factors, such as uncontrolled conditions, treatment compliance, missing data, etc. Still, on population level, a statistically significant mean improvement in ppFEV1 from baseline through the follow-up period was found of 4.53 percentage points (95% CI: 3.50, 5.56). The improvement in ppFEV1 was lower in patients who had previously received CFTR modulator treatment than in patients who had not, likely because of the modulator treatment the latter group had already received.

Expanded French Compassionate Program (FCP)

The FCP was open to a non-F CF population regardless the presence of an FRT responsive mutation. Therefore, this trial likely included the most prevalent non-F CFTR mutations in France, while it also collected data for those CFTR mutations that failed to show a response in the FRT assay.

This observational study showed that the overall population of non-selected non-F pwCF showed an improvement in ppFEV1 (~7.5%) as observed in study CFD-016 (~4.5%) and study 124 (~9.5%).

Overall 61% of pwCF showed a clinical response, an effect that was increased to 96% in the subgroup of pwCF harbouring an FDA-approved, i.e. FRT-responsive CFTR mutation. Relevant improvements in ppFEV1 and SwCl were observed among the responders. Overall, the data are consistent with previous clinical studies and the registries.

By-CFTR-mutation analysis

CF is a recessive disease where both alleles can potentially contribute to the response. With the approval of the F variant, the responsiveness of a non-F variant can only be evaluated in the smaller, but genetically heterogenous group of non-F pwCF. The attribution of the clinical responsiveness to a specific mutation is impaired in the heterozygous patients, as the response can be attributed to both alleles.

- Studies 124, 125 and CFD-016

The by-CFTR-mutation analyses showed the within treatment improvement only and no comparison with placebo was made.

The by-CFTR-mutation analyses of Studies 124 and 125 were overall more or less consistent with the primary analysis, although effects appeared smaller in some mutations and larger in others. The additional subgroup analyses by CFTR mutation from Study CFD-016 support the results of the Study 124 for the 12 reported mutations.

Results of an additional 8 mutations are provided showing variable results (mean (SD)) ranging from -4.0 (7.6) % ppFEV1 for CFTR mutation R74W (n=8) to 7.1 (10.5) % ppFEV1 for CTFR mutation T1036N.

- Expanded French Compassionate program

The expanded French Compassionate Program collected clinical data in non-F patients regardless of the in vitro response in the FRT assay. Therefore, this study also collected for those CFTR mutations that failed to show a response in the FRT assay or had not been evaluated (yet).

In this study, the FCP committee also assessed the CFTR variant responsiveness based on the totality of the provided data. The presence of a second potentially responsive CFTR variant was also taken into account for determining the responsiveness of a specific CFTR variant.

The FCP could only unequivocally determine the responsiveness of a CFTR variant for a minority of cases (15/76 ~20%). For the other included variants either too limited data was available to be conclusive (43/76 ~56%) or these variants were only present in trans with a known responsive variant and could therefore not be categorised (18/76 ~23%).

The FCP included 68 CFTR variants with known in vitro FRT responsiveness, the number could be updated to 76 CFTR variants with the additional provided data set of study U032. The FRT assay showed consistently a high positive predictive value and sensitivity under the various assumptions. The calculated data from the clinical studies showed a sensitivity of ~90% for the ppFEV1 and a positive predictive value of 100% (*Table 10*). When the data from the FCP was used, the sensitivity varied between 0.75 and 0.89 and the PPV between 0.63 and 1.

Overall, the CHMP considered that the results of the CFTR variant analyses in the different studies must be interpreted with caution. CF is a recessive disease where both alleles can potentially contribute to the response. The current allocation of the responsiveness is based on small numbers and pwCF may show variable responses, even among those who harbour two similar alleles, as modifier genes and/or environmental factors also contribute to the clinical response.

The CHMP also noted, that a negative response in the in vitro assay does not preclude a clinical response. The FCP identified in addition to the N1303K mutation, two other CFTR mutations (r334W and R1066C) that provided a clinically relevant response despite that these mutations showed a negative response in the FRT assay.

Discriminatory statistics FRT Assay

Notwithstanding these uncertainties, the response analyses of the various non-F CFTR variants were used to determine the discriminatory statistics of the FRT test. These discriminatory statistics were provided to support the inclusion of the FRT positive variants in section 5.1 of the SmPC.

The clinical development was restricted to those CFTR variants that showed a positive response in the FRT assay. Therefore, most evidence is gathered for the sensitivity and the positive predictive response. However, as the FCP was open to all non-F pwCF, this observational study also provided support for the specificity and negative predictive value, although this evidence is less strong.

N1303K mutation and investigator-initiated studies

The applicant also applies for the inclusion of the N1303K mutation in the indication. The N1303K mutation does not show an in vitro response to the FRT assay but is supported with clinical data obtained from various single arm trials. The clinical data showed consistent improvements in lung function harbouring this mutation, including homozygous N1303K patients and patients with a minimal function allele in trans. However, regression to the mean cannot be excluded.

Additional provided references show an in vitro response to E/T/I for the N1303K mutation in human nasal epithelial cells and rectal organoids[13] [14] [15] . This in vitro data supports the observed clinical efficacy observed in the single arm trials, although they are obtained from other in vitro assays than the FRT

[13] Ensinck MM, De Keersmaecker L, Ramalho AS, et al. Novel CFTR modulator combinations maximise rescue of G85E and N1303K in rectal organoids. ERJ Open Res 2022; 8: 00716- 2021 [DOI: 10.1183/23120541.00716-2021].

[14] Laselva O, Bartlett C, Gunawardena TNA, et al. Rescue of multiple class II CFTR mutations by elexacaftor+tezacaftor+ivacaftor mediated in part by the dual activities of elexacaftor as both corrector and potentiator. Eur Respir J 2021; 57: 2002774 [https://doi.org/10.1183/13993003.02774-2020].

[15] Veit G, Roldan A, Hancock MA,Da Fonte Dillen F, Xu H, Hussein M, Frenkiel S, Matouk E,Velkov T,Lukacs GL. Allosteric folding correction of F508del and rare CFTR mutants by elexacaftortezacaftor-ivacaftor (Trikafta) combination. jciinsight-5-139983.pdf (nih.gov)

assay.
The ppFEV1 response in the absence of a relevant reduction in SwCl is not yet fully understood.

Other, not (yet) investigated CFTR mutations

The currently applied indication is based on in clinical and/or in vitro data for homozygous non-F pwCF. The submitted application covers about 50% of the non-F CF population. Considering that homozygous class I mutations occur in 3-5% in pwCF, there is a small part of the total CF population not covered by clinical and/or in vitro data: ~5% pwCF, i.e. 25% of the non-F CF population.

This implies that a small, but clearly defined subset of pwCF will not get access and/or has delayed access to treatment based on the ultra-rarity of their genetic profile, while this treatment might change the course of their disease and life expectancy. Not all CFTR variants can be tested by the FRT assay, while the current package already includes data of many prevalent non-F mutations in the EU.

In view of the above considerations, the CHMP considered the need to seek expert advice and receive the best available scientific knowledge. An Ad-hoc Expert meeting was conveyed on 28 November 2024 to discuss whether a trial of therapy could be envisaged for patients in which no in vitro/clinical information is feasible and seek expert advice regarding possibility to a priori identify CFTR mutations that would be responsive to the treatment.

Additional expert consultations

The AHEG experts agreed that a "trial of therapy" would be beneficial to allow patients to receive treatment rather than excluding patients with rare mutations for which clinical response/in vitro response is not known. They considered that a potential clinical response can be evaluated over time, and that criteria for responsiveness should be evaluated in a personalised manner.

The AHEG experts considered that, except for class I mutations, it is not possible to a priori identify CFTR mutations that will not be responsive to Kaftrio also referring to the variability in the individual response among patients harbouring the same mutation. The AHEG experts agreed that reliance on the in vitro FRT assay results without clinical data could be acceptable. Some experts mentioned that confirmation with clinical data should be generated after treatment. The experts raised concerns if the indication should be based on the FRT assay performed only by the company, while this test is not being performed by an independent body or in the clinical routine.

CHMP overall conclusion taking into account Ad-hoc Expert advice:

The provided clinical data (RCT and RWD) show that the efficacy and safety in the non-F CF population appear to be comparable with the complementary population pwCF harbouring at least one F mutation. Thus, Kaftrio has a similar, rational mode of action in both these populations.

Subgroup of non -F mutations, pwCF homozygous for class I CFTR mutations (e.g. nonsense mutations, in-frame deletions)

In these patients, (3 to 5% of the overall CF population), the class I CFTR variant does not produce protein, while modulator therapy needs this protein for binding to be effective. Therefore, the homozygous class I mutations are not expected to respond to Kaftrio/Kalydeco therapy. Therefore a warning has been added in sections 4.2 and 4.4 of the SmPC.

Ultra-rare mutations with no available in vitro/clinical data

The CHMP discussed the fact that non-F pwCF with ultra rare untested CFTR variants are not eligible, mostly based on the rarity of their specific genotype, rather than ineffectiveness of the treatment.

Most of these pwCF with two ultra rare non-F CFTR mutations are treated in specialised centres, providing a suitable environment for evaluating the response to Kaftrio in combination with Kalydeco within a reasonable time frame in a personalised manner.

The response to Kaftrio cannot be predicted based on the genetic profile, except for those pwCF harbouring two class I mutation, but clinical in vitro/ ex vivo models are available outside a clinical trial setting enabling the selection of pwCF that will respond to E/T/I.

With an indication restricted on available clinical and/or in vitro data, a treatment would be delayed until sufficient supportive data have been collected, while collection of additional data is difficult due to the rarity of the mutations. Despite the unmet medical need and the established efficacy and safety profile E/T/I, patient access would be denied due to the ultra-rarity of genetic profile.

Therefore taking into account the current scientific knowledge, the CHMP considered appropriate to extrapolate data to ultra-rare non tested mutations and recommended a broader indication than the proposed MAH indication in order to enable access to patients with ultrarare mutation as follows :

Kaftrio: (new proposed indication in bold)

In a combination regimen with ivacaftor for the treatment of cystic fibrosis patients aged 2 years and older **who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2 and 5.1)**

Kalydeco : (new proposed indication in bold)

In a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 and older **have at least one non-class I mutation in the *CFTR* gene (see sections 4.2 and 5.1)**.

The section 5.1 is listing all available clinical and in vitro data from FRT test in a table.

Further the CHMP considered necessary to receive further information in the post marketing setting on ultrarare FRT non tested mutations, therefore, the MAH agreed to provide yearly updates on positive and negative FRT results.

Assessment of paediatric data on clinical efficacy

The proposed indication for the paediatric population could be accepted based on partial extrapolation for the mutations for which clinical benefit was shown.

The study 124 included a total of 31 patients aged 6-12 years, with 23 patients being treated with E/T/I. The subgroup analyses for this age group aligns with the overall reported study results. Although the overall data is limited, the provided paediatric data align with the data obtained in the adult population.

It is also agreed to extrapolate the results observed in children over 6 years to the younger age group of patients from 2 years of age.

2.4.3. Conclusions on the clinical efficacy

Clinically relevant improvements on all primary and secondary endpoints were achieved in subjects with at least one of 18 non-*F508del* CFTR mutations included in Study 124 in response to treatment with ELX/TEZ/IVA compared to placebo.

Additional supportive data is provided by the extension study, and real-world data of the US CFFPR registry and bibliographical data of the French Compassionate Program.

Although the FRT assay is not considered an EU qualified assay, the US CFFPR and FCP provided further evidence that relevant clinical responses could be achieved in pwCF harbouring at least one, in vitro FRT responsive CFTR mutation.

Additional bibliographical data obtained for the N1303K mutation and results of the FCP show, that a negative FRT assay must be interpreted with caution as at least 3 mutations were identified that showed a clinical response, despite a negative result in the vitro FRT assay. Therefore, a lack of response in the FRT assay does not preclude a potential clinical response. Overall, the FRT assay is considered indicative of a clinical response.

The observed improvements for the non-F pwCF were in line with previous data observed in the heterozygous pwCF population. The current application provides supportive data for ~75% of the non-F pwCF.

Considering the rarity of the remaining, genetically heterogenous, non-F pwCF population, the mode of action, and the totality of the provided data (including the data obtained in the heterozygous F508del population) an all-comers indication excluding modulator non responder patients (homozygous non F patients with class I mutations) -is recommended, with additional comments in Sections 4.2 and 5.1.

The applicant agreed to exclude from section 5.1 the CFTR variants that are non-CF causing. CF is a recessive disease and requires that both alleles are affected. Although these mutations show a response, we consider that they should not be included in the SmPC as CF is a recessive disease and at least 2 alleles should be affected. Patients harbouring a non-CF causing mutation may have a higher risk that they will be incorrectly diagnosed with CF when these mutations are included in section 5.1 of the SmPC. These patients usually have mild organ system manifestation that does not typically meet diagnostic criteria for CF.[16]

The CHMP agreed indication is:

Kaftrio: (new proposed indication in bold)

In a combination regimen with ivacaftor for the treatment of cystic fibrosis patients aged 2 years and older **who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2 and 5.1)**

Kalydeco : (new proposed indication in bold)

In a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 and older **have at least one non-class I mutation in the *CFTR* gene (see sections 4.2 and 5.1)**.

In the post marketing setting, yearly updates on positive and negative FRT results will be provided by the MAH.

[16] Sosnay PR, Salinas D, White TB et al. Applying Cystic Fibrosis Transmembrane Conductance Regulator Genetics and CFTR2 Data to facilitate diagnosis. J Pediatr 2017; 181S: S27032

2.5. Clinical safety

Introduction

So far, the safety profile of ELX/TEZ/IVA is based on data from more than 3,328 subjects treated with ELX/TEZ/IVA for varying durations up to 4 years. ELX/TEZ/IVA is generally safe and well tolerated in CF patients ≥2 years of age with a low rate of adverse events (AEs) leading to treatment discontinuation. Overall, AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects.

Adverse drug reactions (ADRs) for ELX/TEZ/IVA include upper respiratory tract infection, headache, nasal congestion, rhinorrhoea, diarrhoea, abdominal pain, rash, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, blood creatinine kinase (CK) increased, and increased blood pressure. ADRs are generally mild or moderate in severity and can be readily recognised, monitored, and managed.

Important identified risks are susceptibility for influenza virus infections and hepatotoxicity and an important potential risk is cataract.

The safety profile of ELX/TEZ/IVA is similar across subgroups of subjects with CF, including age, sex, and ppFEV1. Extensive data indicate that the safety profile is consistent across subjects with different CFTR genotypes (i.e., F/F, F/MF, F/Gating, F/RF).

Safety data includes Study 124 are submitted with in support, the publications by Solomon et al.[17] Sadras et al.[18] and Burgel et al.[19].

The submitted non-interventional RWE data from US patients with ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations receiving commercially available ELX/TEZ/IVA (Study CFD-016) do not contain safety data.

Patient exposure

Study 124 Safety Set included all subjects who received at least 1 dose of study drug. A total of 307 subjects received at least 1 dose of study drug. The exposure was similar between treatment groups. The mean exposure was 23.3 weeks in the ELX/TEZ/IVA group and 24.1 weeks in the placebo group.

[17] Solomon G. Oral Presentation: Interim results of an open-label trial to evaluate ETI in individuals with cystic fibrosis and an N1303K mutation who are not eligible for modulator treatment. Presented at: 2023 North American Cystic Fibrosis Conference, 03 November 2023, Phoenix, AZ.
[18] Sadras I, Kerem E, Livnat G, Sarouk I, Breuer O, Reiter J, et al. Clinical and functional efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis carrying the N1303K mutation. J Cyst Fibros. 2023;S1569-1993(23):00178-9.
[19] Burgel PR, Sermet-Gaudelus I, Durieu I, Kanaan R, Macey J, Grenet D, et al. The French Compassionate Program of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del CFTR variant. Eur Respir J. 2023;Online Ahead of Print:1-27.

Table *26* summarises the extent of exposure to study drug in the Study 124 Treatment period.

Table 26: Study 124 summary of exposure, Safety Set for the Treatment period

Category	Placebo N = 102	ELX/TEZ/IVA N = 205
Total exposure (patient weeks)	2453.7	4784.1
Total exposure (patient years)	51.1	99.7
Exposure duration (weeks)		
n	102	205
Mean (SD)	24.1 (0.5)	23.3 (3.3)
Median	24.0	24.0
Min, max	22.6, 25.9	1.6, 26.3
Exposure duration by interval, n (%)		
≤1 week	0	0
>1 to ≤2 weeks	0	1 (0.5)
>2 to ≤4 weeks	0	1 (0.5)
>4 to ≤8 weeks	0	3 (1.5)
>8 to ≤12 weeks	0	1 (0.5)
>12 to ≤16 weeks	0	1 (0.5)
>16 to ≤20 weeks	0	0
>20 to ≤24 weeks	60 (58.8)	134 (65.4)
>24 weeks	42 (41.2)	64 (31.2)

Source: Study 124 CSR/Table 12-1
ELX: elexacaftor; IVA: ivacaftor; N: total sample size; n: size of subsample; 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 of study drug– first dose date + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = Duration of study drug exposure (weeks)/48; 1 year = 48 weeks.

Adverse events

The proportion of subjects with at least 1 AE was 94.1% in the ELX/TEZ/IVA group and 95.1% in the placebo group. Serious AEs (SAEs) occurred in 18 (8.8%) subjects in the ELX/TEZ/IVA group and 15 (14.7%) subjects in the placebo group. The majority of AEs were mild or moderate in severity. Severe AEs occurred in 15 (7.3%) subjects in the ELX/TEZ/IVA group and 12 (11.8%) subjects in the placebo group. No subjects in either group had a life-threatening AE. One (0.5%) subject in the ELX/TEZ/IVA group died due to an SAE of lung adenocarcinoma that was considered not related to study drug. (**Table 27**).

Table 27: Study 124 overview of Adverse Events (Safety Set)

	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Number of AEs (total)	528	1187
Subjects with any AEs	97 (95.1)	193 (94.1)
Subjects with AEs by strongest relationship		
Not related	54 (52.9)	55 (26.8)
Unlikely related	14 (13.7)	13 (6.3)
Possibly related	27 (26.5)	98 (47.8)
Related	2 (2.0)	27 (13.2)
Subjects with AEs by maximum severity		
Mild	46 (45.1)	85 (41.5)
Moderate	39 (38.2)	92 (44.9)
Severe	12 (11.8)	15 (7.3)
Life-threatening	0	0
Death	0	1 (0.5)
Missing	0	0
Subjects with AEs leading to study drug discontinuation	0	5 (2.4)
Subjects with AEs leading to study drug interruption	1 (1.0)	25 (12.2)
Subjects with Grade 3/4/5 AEs	12 (11.8)	16 (7.8)
Subjects with related AEs[a]	29 (28.4)	125 (61.0)
Subjects with SAEs	15 (14.7)	18 (8.8)
Subjects with related SAEs[a]	0	2 (1.0)
Subjects with AEs leading to death	0	1 (0.5)

Source: Module 2.7.4/Table 3

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.

Common Adverse Events

AEs occurring in ≥10% of subjects in the ELX/TEZ/IVA group were rash, nasopharyngitis, headache, cough, infective pulmonary exacerbation (PEx) of CF, pyrexia, and diarrhoea. These events were generally consistent with common manifestations of CF disease and the established ELX/TEZ/IVA safety profile. AEs occurring in ≥10% of subjects in the placebo group were infective PEx of CF, cough, nasopharyngitis, pyrexia, headache, sputum increased, and abdominal pain.

There was a higher incidence of rash events in the ELX/TEZ/IVA group, that is discussed in greater detail in Section AESI. There was also a higher incidence of influenza events in the ELX/TEZ/IVA group compared to the placebo group. In the ELX/TEZ/IVA group, all of the AEs of influenza were considered not related to study drug by the investigator, and none led to change in study drug dosing. There was also a lower rate of AEs reported in the SOC infections and infestations in the ELX/TEZ/IVA group as compared to the placebo group. Overall, this suggests that the higher incidence of influenza in the ELX/TEZ/IVA group is likely an incidental finding and not related to study drug.

AEs that occurred in at least 5% of subjects in any treatment group are summarized by PT in **Table 28**.

Table 28: Study 124 AEs occurring in at least 5% of subjects in any treatment group, Safety Set

Preferred Term	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Subjects with any AEs	97 (95.1)	193 (94.1)
Rash	1 (1.0)	45 (22.0)
Nasopharyngitis	20 (19.6)	42 (20.5)
Headache	13 (12.7)	37 (18.0)
Cough	26 (25.5)	36 (17.6)
Infective PEx of CF	37 (36.3)	31 (15.1)
Pyrexia	14 (13.7)	27 (13.2)
Diarrhea	10 (9.8)	26 (12.7)
Rhinitis	6 (5.9)	20 (9.8)
Sputum increased	13 (12.7)	20 (9.8)
COVID-19	10 (9.8)	19 (9.3)
Influenza	2 (2.0)	18 (8.8)
Abdominal pain	13 (12.7)	17 (8.3)
Oropharyngeal pain	10 (9.8)	17 (8.3)
Upper respiratory tract infection	10 (9.8)	17 (8.3)
Constipation	4 (3.9)	15 (7.3)
Vomiting	7 (6.9)	15 (7.3)
Hemoptysis	6 (5.9)	12 (5.9)
Abdominal pain upper	7 (6.9)	10 (4.9)
Nasal congestion	8 (7.8)	6 (2.9)
Productive cough	6 (5.9)	6 (2.9)

Source: Study 124 CSR/Table 12-3
AE: adverse event; CF: cystic fibrosis; COVID-19: coronavirus disease; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor
Note: AEs were coded using MedDRA version 26.0. A subject with multiple events within a category was counted only once in that category. Table was sorted in descending order of frequency of the ELX/TEZ/IVA column by PT.

Severity of Adverse Events

The majority of subjects overall had AEs that were mild (42.7%) or moderate (42.7%) in severity.

In the ELX/TEZ/IVA group, 15 (7.3%) subjects had severe AEs and no subjects had life-threatening AEs. In the placebo group, 12 (11.8%) subjects had severe AEs and no subjects had life-threatening AEs. One (0.5%) subject in the ELX/TEZ/IVA group died due to an AE of lung adenocarcinoma that was considered not related to study drug treatment.

Grade 3/4/5 AEs are presented by SOC and PT in **Table 29**.

Table 29: Grade 3/4/5 TEAEs by System Organ Class and Preferred Term Safety Set

System Organ Class Preferred Term	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Subjects with any Grade 3/4/5 TEAEs	12 (11.8)	16 (7.8)
Infections and infestations	11 (10.8)	7 (3.4)
Infective pulmonary exacerbation of cystic fibrosis	11 (10.8)	4 (2.0)
Bronchopulmonary aspergillosis allergic	0	2 (1.0)
Pneumonia	0	1 (0.5)
Pseudomonas infection	0	1 (0.5)
Bronchopulmonary aspergillosis	1 (1.0)	0
Skin and subcutaneous tissue disorders	0	5 (2.4)
Rash	0	4 (2.0)
Rash maculo-papular	0	1 (0.5)
Musculoskeletal and connective tissue disorders	0	2 (1.0)
Exertional rhabdomyolysis	0	1 (0.5)
Polyarthritis	0	1 (0.5)
Gastrointestinal disorders	0	1 (0.5)
Pancreatitis	0	1 (0.5)
Subileus	0	1 (0.5)
Hepatobiliary disorders	0	1 (0.5)
Cholecystitis acute	0	1 (0.5)
Investigations	1 (1.0)	1 (0.5)
Blood creatine phosphokinase increased	0	1 (0.5)
Magnetic resonance imaging thoracic abnormal	1 (1.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5)
Lung adenocarcinoma	0	1 (0.5)
Psychiatric disorders	0	1 (0.5)
Anxiety disorder	0	1 (0.5)
Post-traumatic stress disorder	0	1 (0.5)
Cardiac disorders	1 (1.0)	0
Stress cardiomyopathy	1 (1.0)	0
Respiratory, thoracic and mediastinal disorders	1 (1.0)	0
Bronchial secretion retention	1 (1.0)	0
Bronchiectasis	1 (1.0)	0

- MedDRA version 26.0.
- 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.

Relationship of Adverse Events

Twenty-seven (13.2%) subjects in the ELX/TEZ/IVA group and 2 (2.0%) subjects in the placebo group had an AE assessed by the investigator as related; 98 (47.8%) subjects in the ELX/TEZ/IVA group and 27 (26.5%) subjects in the placebo group had an AE assessed by the investigator as possibly related (**Table 30**).

Table 30: Related AEs occurring in ≥5 subjects in any treatment group (Safety Set)

System Organ Class Preferred Term	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Subjects with any related AEs	29 (28.4)	125 (61.0)
Skin and subcutaneous tissue disorders	2 (2.0)	57 (27.8)
Rash	1 (1.0)	41 (20.0)
Pruritus	1 (1.0)	6 (2.9)
Gastrointestinal disorders	15 (14.7)	39 (19.0)
Diarrhea	4 (3.9)	14 (6.8)
Constipation	0	10 (4.9)
Abdominal pain upper	4 (3.9)	8 (3.9)
Abdominal pain	4 (3.9)	6 (2.9)
Investigations	3 (2.9)	20 (9.8)
Blood bilirubin increased	0	8 (3.9)
ALT increased	0	7 (3.4)
AST increased	0	7 (3.4)
Blood CK increased	2 (2.0)	5 (2.4)
Nervous system disorders	8 (7.8)	20 (9.8)
Headache	5 (4.9)	15 (7.3)
Respiratory, thoracic and mediastinal disorders	7 (6.9)	20 (9.8)
Sputum increased	3 (2.9)	9 (4.4)
Cough	2 (2.0)	7 (3.4)
Psychiatric disorders	0	17 (8.3)
Insomnia	0	8 (3.9)

Source: Table 14.3.1.6

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class; TEZ: tezacaftor

Note: AEs were coded using MedDRA version 26.0. A subject with multiple events within a category was counted only once in that category. Table was sorted in descending order of frequency of the ELX/TEZ/IVA column by SOC, and by PT within each SOC. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted.

Serious adverse event/deaths/other significant events

Deaths

There was 1 (0.5%) subject in the ELX/TEZ/IVA group who died due to an AE of lung adenocarcinoma that was considered not related to study drug treatment.

Serious adverse event

Eighteen (8.8%) subjects in the ELX/TEZ/IVA group and 15 (14.7%) subjects in the placebo group had at least 1 SAE. SAEs that occurred in ≥2 subjects in the ELX/TEZ/IVA group included infective PEx of CF (5 subjects) and bronchopulmonary aspergillosis allergic (2 subjects). The only SAE that occurred in ≥2 subjects in the placebo group was infective PEx of CF (13 subjects).

Overall, the SAEs were mostly consistent with common manifestations or complications in CF subjects ≥6 years of age and the known ELX/TEZ/IVA safety profile.

The majority of SAEs were assessed by the investigator as unlikely related or not related to study drug.

Table 31: Serious TEAEs by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Subjects with any serious TEAEs	15 (14.7)	18 (8.8)
Infections and infestations	13 (12.7)	11 (5.4)
Infective pulmonary exacerbation of cystic fibrosis	13 (12.7)	5 (2.4)
Bronchopulmonary aspergillosis allergic	0	2 (1.0)
Gastroenteritis	0	1 (0.5)
Hepatitis viral	0	1 (0.5)
Pneumonia	0	1 (0.5)
Pseudomonas infection	0	1 (0.5)
Vestibular neuronitis	0	1 (0.5)
Gastrointestinal disorders	0	2 (1.0)
Abdominal pain	0	1 (0.5)
Pancreatitis	0	1 (0.5)
Subileus	0	1 (0.5)
Hepatobiliary disorders	0	1 (0.5)
Cholecystitis acute	0	1 (0.5)
Metabolism and nutrition disorders	0	1 (0.5)
Dehydration	0	1 (0.5)
Musculoskeletal and connective tissue disorders	0	1 (0.5)
Polyarthritis	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5)
Lung adenocarcinoma	0	1 (0.5)
Psychiatric disorders	0	1 (0.5)
Anxiety disorder	0	1 (0.5)
Post-traumatic stress disorder	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0	1 (0.5)
Haemoptysis	0	1 (0.5)
Skin and subcutaneous tissue disorders	0	1 (0.5)
Rash maculo-papular	0	1 (0.5)
Cardiac disorders	1 (1.0)	0
Stress cardiomyopathy	1 (1.0)	0
General disorders and administration site conditions	1 (1.0)	0
Drug intolerance	1 (1.0)	0
Renal and urinary disorders	1 (1.0)	0
Renal colic	1 (1.0)	0

- MedDRA version 26.0.
- 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.

Related serious adverse event

Two (1.0%) subjects in the ELX/TEZ/IVA group and no subjects in the placebo group had at least 1 related SAE. SAEs that occurred in the ELX/TEZ/IVA group included subileus (1 subject) and rash maculo-papular.

Adverse Events of Special Interest

AEs of special interest (AESIs) were defined as AEs of elevated transaminases and AEs of rash.

Transaminase Elevations

Elevated transaminase events are summarised in **Table 32**.

Elevated transaminase events occurred in 8 (3.9%) subjects in the ELX/TEZ/IVA group and no subjects in the placebo group. All elevated transaminase events were mild or moderate in severity, and none were serious.

In the ELX/TEZ/IVA group, 1 (0.5%) subject had elevated transaminase events that led to treatment discontinuation. Three (1.5%) subjects had elevated transaminase events that led to treatment interruption. The median time to onset of first elevated transaminase event was 82.5 (range: 15 to 166) days. The median duration of elevated transaminase events was 16.0 (range: 8 to 22) days.

Overall, AESIs of transaminase events in Study 124 were consistent with prior experience.

Table 32: Study 124 summary of elevated transaminase events (Safety Set)

Category	Placebo N = 102	ELX/TEZ/IVA N = 205
Subjects with any events	0	8 (3.9)
ALT increased	0	8 (3.9)
AST increased	0	8 (3.9)
Subjects with any events by maximum severity		
Mild	0	4 (2.0)
Moderate	0	4 (2.0)
Subjects with events leading to treatment discontinuation, n (%)	0	1 (0.5)
Subjects with events leading to treatment interruption, n (%)	0	3 (1.5)
Subjects with serious events, n (%)	0	0
Subjects with related serious events[a], n (%)	0	0
Subjects with events leading to death, n (%)	0	0
Duration of events (days)[b]		
Number of events	0	20
Number of events with non-missing duration	0	12
Mean (SD)	-- (--)	15.8 (4.9)
Median	--	16.0
Min, max	--, --	8, 22
Time-to-onset of first event (days)[c]		
Subjects with event with complete start date	0	8
Mean (SD)	-- (--)	84.4 (59.8)
Median	--	82.5
Min, max	--, --	15, 166

Source: Study 124 CSR/Table 14.3.2.8
ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; IVA: ivacaftor; N: total sample size; n: size of subsample; PT: Preferred Term; TEZ: tezacaftor
Notes: MedDRA version 26.0 was used. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. PTs are sorted by alphabetical order.
[a] Includes events with relationship of related, possibly related, and missing.
[b] Duration was only calculated for events with complete start and end dates.
[c] Time-to-onset was only calculated for events with complete start date.

In response to the request for supplementary information, the MAH conducted a review of all hepatic events, including AEs under SOC "Hepatobiliary Disorders" and additional preferred terms (PT) within the

SMQs "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "Liver- related investigations, signs, and symptoms," "Hepatitis, non-infectious," and "Cholestasis and jaundice of hepatic origin". Table 33 lists the hepatic AEs by PT that occurred in subjects in Study 124. Four hepatic AEs were reported in 4 patients: acute cholecystitis (assessed by the investigator as severe and unlikely related to study drug), hepatic cytolysis (moderate and possibly related), CF hepatic disease (mild, possibly related) and a SAE of hepatitis viral (severe, likely confounded by enterovirus).

Table 33. Summary of Treatment-emergent Hepatic Events (Safety Set, Study 124)

Preferred Term	Placebo N = 102	ELX/TEZ/IVA N = 205
Subjects with any events, n (%)	0	19 (9.3)
Alanine aminotransferase increased	0	8 (3.9)
Aspartate aminotransferase increased	0	8 (3.9)
Blood bilirubin increased	0	8 (3.9)
Bilirubin conjugated increased	0	4 (2.0)
Blood bilirubin unconjugated increased	0	4 (2.0)
Gamma-glutamyltransferase increased	0	4 (2.0)
Cholecystitis acute	0	1 (0.5)
Cystic fibrosis hepatic disease	0	1 (0.5)
Hepatic cytolysis	0	1 (0.5)
Hepatitis viral	0	1 (0.5)

Source: Ad hoc Table 14.3.2.8.2

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor
Notes: Hepatic events were coded using MedDRA version 26.0. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category is counted only once in that category. PTs are sorted by the order of frequency of the ELX/TEZ/IVA column and then alphabetical order within the same frequency by PT.

Rash

Rash events occurred in 55 (26.8%) subjects in the ELX/TEZ/IVA group and 3 (2.9%) subjects in the placebo group. The majority of rash events were mild or moderate in severity.

One (0.5%) subject in the ELX/TEZ/IVA group had a serious rash event that was considered related to study drug and led to treatment discontinuation; 15 (7.3%) subjects in the ELX/TEZ/IVA group had rash events that led to treatment interruption. No subjects in the placebo group had rash events that led to treatment discontinuation or interruption.

The median time-to-onset of first rash event was 11.0 (range: 2 to 168) days in the ELX/TEZ/IVA group and 57.0 (range: 27 to 150) days in the placebo group. The median duration of rash events was 9.5 (range: 1 to 110) days in the ELX/TEZ/IVA group and 37.0 (range: 1 to 57) days in the placebo group.

Table 34: Study 124 summary of treatment-emergent rash events (Safety Set)

	Placebo N = 102	ELX/TEZ/IVA N = 205
Subjects with any events, n (%)	3 (2.9)	55 (26.8)
Dermatitis atopic	0	1 (0.5)
Drug hypersensitivity	1 (1.0)	0
Rash	1 (1.0)	45 (22.0)
Rash erythematous	0	1 (0.5)
Rash maculo-papular	0	2 (1.0)
Rash papular	1 (1.0)	1 (0.5)
Skin exfoliation	0	1 (0.5)
Urticaria	0	6 (2.9)
Subjects with any events by maximum severity, n (%)		
Mild	2 (2.0)	27 (13.2)
Moderate	1 (1.0)	23 (11.2)
Severe	0	5 (2.4)
Life-threatening	0	0
Death	0	0
Missing	0	0
Subjects with events leading to treatment discontinuation, n (%)	0	1 (0.5)
Subjects with events leading to treatment interruption, n (%)	0	15 (7.3)
Subjects with serious events, n (%)	0	1 (0.5)
Subjects with related serious events, n (%)[a]	0	1 (0.5)
Subjects with events leading to death, n (%)	0	0
Time-to-onset of first event (days)[b]		
Subjects with event with complete start date	3	55
Mean (SD)	78.0 (64.1)	25.0 (39.1)
Median	57.0	11.0
Min, max	27, 150	2, 168
Duration of events (days)[b]		
Number of events	4	63
Number of events with duration	4	58
Mean (SD)	33.0 (23.3)	15.3 (18.4)
Median	37.0	9.5
Min, max	1, 57	1, 110

Source: Study 124 CSR/Table 12-5

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

Notes: Events were coded using MedDRA version 26.0. When summarizing number of events, a subject with multiple events 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. PTs were sorted by alphabetical order.

[a] Related SAEs included related, possibly related, and missing categories.

[b] The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date.

By sex, 34 of 113 female subjects (30.1%) and 21 of 92 male subjects (22.8%) in the ELX/TEZ/IVA group had rash events, and 2 of 52 female subjects (3.8%) and 1 of 50 male subjects (2.0%) in the placebo group had rash events.

In female subjects receiving ELX/TEZ/IVA, 10 of 25 subjects (40.0%) who used hormonal therapy during the study and 24 of 88 subjects (27.3%) not using hormonal therapy had rash events. In female subjects receiving placebo, no subjects who used hormonal therapy and 2 of 42 subjects (4.8%) not using hormonal therapy had rash events.

Laboratory findings

Chemistry

Liver Function Tests

Mean concentrations of LFT parameters were variable over time in both groups. In the ELX/TEZ/IVA group, increases from baseline in mean ALT and AST were observed. The mean (SD) increase in ALT ranged from 2.3 (19.7) U/L at Day 15 to 5.6 (25.0) U/L at Week 24.

The mean (SD) increase in AST ranged from 2.7 (11.0) U/L at Week 8 to 5.5 (25.1) U/L at Week 24. In the placebo group, there were no trends in ALT or AST. There were no trends in mean ALP or GGT values in either group.

The majority of subjects had ALT and AST values that remained within the normal range (**Table *35***). ALT or AST >3, >5, and >8 × ULN occurred in 13 (6.3%), 4 (2.0%), and 4 (2.0%) subjects in the ELX/TEZ/IVA group, respectively. No subject in the placebo group had ALT or AST >3× ULN. No subject in either group had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN.

Four (2.0%) subjects in the ELX/TEZ/IVA group and no subjects in the placebo group had AEs of GGT increased. In the ELX/TEZ/IVA group, 1 subject had an AE of GGT increased that led to treatment discontinuation (after treatment interruption) and 2 subjects had AEs of GGT increased that led to treatment interruption. No subject in either group had AEs of ALP increased.

Table 35: Study 124 threshold analysis of LFT chemistry parameters during the TE period (Safety Set)

Parameter Subjects with Non-missing Post-baseline Data Post-baseline Threshold Analysis Criteria, n (%)	Placebo N = 102	ELX/TEZ/IVA N = 205
ALT (U/L)		
Total, N1	102	205
>ULN to ≤3 × ULN	13 (12.7)	38 (18.5)
>3 × to ≤5 × ULN	0	8 (3.9)
>5 × to ≤8 × ULN	0	1 (0.5)
>8 × to ≤20 × ULN	0	1 (0.5)
>20 × ULN	0	0
>3 × ULN	0	10 (4.9)
>5 × ULN	0	2 (1.0)
>8 × ULN	0	1 (0.5)
AST (U/L)		
Total, N1	102	205
>ULN to ≤3 × ULN	16 (15.7)	42 (20.5)
>3 × to ≤5 × ULN	0	7 (3.4)
>5 × to ≤8 × ULN	0	0
>8 × to ≤20 × ULN	0	3 (1.5)
>20 × ULN	0	0
>3 × ULN	0	10 (4.9)
>5 × ULN	0	3 (1.5)
>8 × ULN	0	3 (1.5)
ALT (U/L) or AST (U/L)		
Total, N1	102	205
(ALT>ULN to ≤3 × ULN) or (AST>ULN to ≤3 × ULN)	22 (21.6)	59 (28.8)
(ALT>3 × to ≤5 × ULN) or (AST>3 × to ≤5 × ULN)	0	9 (4.4)
(ALT>5 × to ≤8 × ULN) or (AST>5 × to ≤8 × ULN)	0	0
(ALT>8 × to ≤20 × ULN) or (AST>8 × to ≤20 × ULN)	0	4 (2.0)
ALT>20 × ULN or AST>20 × ULN	0	0
(ALT>3 × ULN) or (AST>3 × ULN)	0	13 (6.3)
(ALT>5 × ULN) or (AST>5 × ULN)	0	4 (2.0)
(ALT>8 × ULN) or (AST>8 × ULN)	0	4 (2.0)
TBILI (µmol/L)		
Total, N1	102	205
>ULN to ≤1.5 × ULN	7 (6.9)	33 (16.1)
>1.5 × to ≤2 × ULN	3 (2.9)	9 (4.4)
>2 × to ≤3 × ULN	1 (1.0)	5 (2.4)
>3 × to ≤10 × ULN	0	0
>10 × ULN	0	0
(ALT or AST) and TBILI		
Total, N1	102	205
(ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN	0	0
ALP (U/L)		
Total, N1	102	205
>ULN to ≤1.5 × ULN	7 (6.9)	17 (8.3)
>1.5 × to ≤2.5 × ULN	0	5 (2.4)
>2.5 × to ≤5 × ULN	0	0
>5 × to ≤20 × ULN	0	0
>20 × ULN	0	0
GGT (U/L)		
Total, N1	102	205
>ULN to ≤2.5 × ULN	4 (3.9)	25 (12.2)
>2.5 × to ≤5 × ULN	0	3 (1.5)
>5 × to ≤20 × ULN	0	0
>20 × ULN	0	0

Source: Table 14.3.4.2

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; 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. Percentages were evaluated as n/N1. Threshold criteria involving 2 LFT parameters could be determined by assessments at different visits during the TE Period.

The majority of subjects had ALT and AST values that remained within the normal range. The number of subjects with ALT or AST >3 was low (6.3%). No subject in either group had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN. The observed events rate is consistent with consistent with prior experience.

Creatine Kinase

The mean CK concentration was variable over time in both groups. In the ELX/TEZ/IVA group, increases from baseline in mean CK were observed. The mean (SD) increase in CK ranged from 38.1 (193.9) U/L at Week 4 to 340.7 (4295.9) U/L at Day 15. The high mean CK value at Day 15 was due to an outlier, which is observed in the high SD value. In the placebo group, there were no trends in CK. The majority of subjects had CK levels that remained within the normal range.

Eleven (5.4%) subjects in the ELX/TEZ/IVA group had CK >5 × ULN, including 5 (2.4%) subjects with CK >10 × ULN. One (1.0%) subject in the placebo group had CK >10 × ULN. All subjects with elevations >10 × ULN had exercised before the elevations.

Table 36: Study 124 threshold analysis of non-LFT chemistry during the TE period (Safety Set)

Parameter Subjects with Non-missing Post-baseline Data Post-baseline Threshold Analysis Criteria, n (%)	Placebo N = 102	ELX/TEZ/IVA N = 205
Creatine kinase (U/L)		
Total, N1	102	205
>ULN to ≤2.5xULN	22 (21.6)	66 (32.2)
>2.5x to ≤5xULN	2 (2.0)	11 (5.4)
>5x to ≤10xULN	0	6 (2.9)
>10xULN	1 (1.0)	5 (2.4)

- N1: the number of subjects with at least one non-missing measurement during the treatment-emergent period.
- n is the number of subjects in the post-baseline category; within each parameter, a subject is counted in all applicable post-baseline categories based on the worst assessment during the treatment-emergent period; percentage is n/N1.

AEs of blood creatine phosphokinase increased occurred in 7 (3.4%) subjects in the ELX/TEZ/IVA group and 3 (2.9%) subjects in the placebo group. In the ELX/TEZ/IVA group, 1 (0.5%) subject had an AE of rhabdomyolysis, which presented with blood creatine phosphokinase elevation but did not have features consistent with rhabdomyolysis (e.g., kidney involvement, myoglobinuria) and was attributed to heavy exercise in the prior 72 hours; 1 (0.5%) subject in the ELX/TEZ/IVA group had an AE of exertional rhabdomyolysis that led to treatment interruption, also presented with blood creatine phosphokinase elevation, did not have features consistent with rhabdomyolysis (e.g., kidney involvement), and was attributed to heavy exercise in the prior 72 hours. No subjects in the placebo group had an AE of rhabdomyolysis.

The AEs of blood creatine phosphokinase were mostly mild or moderate; AEs were of severe intensity in 1 subject in the ELX/TEZ/IVA group and no subjects in the placebo group. None of the AEs were serious.

AEs of blood creatine phosphokinase increased led to study drug interruption in 1 (0.5%) subject in the ELX/TEZ/IVA group and no subjects in the placebo group. Most CK elevations resolved without change to study drug dosing or after treatment interruption. One (0.5%) subject in the ELX/TEZ/IVA group discontinued treatment due to an AE of blood creatine phosphokinase increased.

The majority of subjects had CK values that remained within the normal range. The number of subjects with CK > 2.5 x ULN was low (5.4%). The observed event rate is consistent with consistent with prior experience.

Other chemistry parameters

There were no trends in other chemistry parameters.

Haematology

Mean concentrations of haematology parameters were variable over time in both groups. In the ELX/TEZ/IVA group, decreases from baseline in mean platelets, leukocytes, and neutrophils were observed. Mean values of these parameters remained within normal limits at all assessed time points. The mean (SD) decrease in platelets ranged from -10.6 (57.5) × 109/L on Day 15 to -20.7 (65.7) × 109/L at Week 24. The mean (SD) decrease in leukocytes ranged from -0.59 (2.26) × 109/L at Day 15 to -1.35 (2.57) × 109/L at Week 24. The mean (SD) decrease in neutrophils ranged from -0.64 (2.16) × 109/L at Day 15 to -1.18 (2.41) × 109/L at Week 24.

There were no trends observed in other haematology parameters in the ELX/TEZ/IVA group. In the placebo group, there were no trends in any of the haematology parameters.

Overall, AEs related to haematology were infrequent (most PTs occurred in 1 to 2 subjects each) with a similar overall incidence across treatment groups. None of the AEs related to haematology were serious or led to treatment discontinuation or interruption.

Coagulation

There were no trends in coagulation assessments.

AEs related to coagulation were infrequent (most PTs occurred in 1 to 2 subjects each) with a similar overall incidence across treatment groups. None of the AEs related to coagulation were serious or led to treatment discontinuation or interruption.

Urinalysis

There were no trends in urinalysis results. AEs related to urinalysis were infrequent (most PTs occurred in 1 to 2 subjects each) with a similar overall incidence across treatment groups. None of the AEs related to urinalysis were serious or led to treatment discontinuation or interruption.

Vital signs, ECGs, or pulse oximetry

There were no clinically relevant trends in other laboratory values, vital signs, ECGs, or pulse oximetry.

Safety in special populations

A total of 6 patients in Study 124 was 65 years of age or older, of whom 5 were treated with ELX/TEZ/IVA (Table 37). All 6 patients had at least 1 AE during the TE period. Most AEs were considered mild or moderate in severity; 1 subject in the ELX/TEZ/IVA group had 1 severe AE and 1 fatal AE of unrelated lung adenocarcinoma that led to study drug discontinuation and was not considered related to study drug.

Table 37: Safety information for patients ≥65 Years of Age at Baseline

	ELX/TEZ/IVA N = 205				Placebo N = 102			
MedDRA terms	**Age <65** N (%)	**Age 65-74** N (%)	**Age 75-84** N (%)	**Age 85+** N (%)	**Age <65** N (%)	**Age 65-74** N (%)	**Age 75-84** N (%)	**Age 85+** N (%)
Number of subjects (%)	200 (97.6)	5 (2.4)	0	0	101 (99.0)	0	0	1 (1.0)
Total numbers of AEs	1187				528			
Total numbers of AEs per age group (% of total number of TEAEs)	1165 (98.1)	22 (1.9)	0	0	523 (99.1)	0	0	5 (0.9)
SAEs - Total	24				22			
SAEs – Total per age group (% of total number of SAEs)[a]	22 (91.7)	2 (8.3)	0	0	22 (100.0)	0	0	0
Fatal	0	1 (4.2)	0	0	0	0	0	0
Hospitalization/ prolong existing hospitalization	21 (87.5)	2 (8.3)	0	0	22 (100.0)	0	0	0
Life-threatening	0	0	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	3 (12.5)	1 (4.2)	0	0	0	0	0	0

Safety in paediatric patients 6-11 years old

A total of 31 patients in Study 124 were 6 through 11 years of age, of whom 23 received ELX/TEZ/IVA (**Table *38***, **Table *39***). There were no Grade 3/4/5 AEs and 1 patient discontinued treatment due to an AE of diarrhoea of moderate severity. In total 2 SAEs were reported for the ELX/TEZ/IVA arm vs. none in the placebo arm. One SAE was (entero)viral hepatitis. The other SAE was a case of infective PEx of CF that led to hospitalization in a 9-year-old patient. Study drug dosing was not changed due to the event and the event resolved after treatment. The SAE was considered by the investigator to be moderate in intensity and not related to study drug.

Table 38: Summary of AEs for Patients 6 through 11 Years of Age at Baseline (Safety Set, Study 124)

	Placebo N = 8 n (%)	ELX/TEZ/IVA N = 23 n (%)	Total N = 31 n (%)
Number of AEs (total)	52	119	171
Subjects with any AEs	8 (100.0)	23 (100.0)	31 (100.0)
Subjects with AEs by strongest relationship			
Not related	4 (50.0)	8 (34.8)	12 (38.7)
Unlikely related	0	3 (13.0)	3 (9.7)
Possibly related	4 (50.0)	8 (34.8)	12 (38.7)
Related	0	4 (17.4)	4 (12.9)
Subjects with AEs by maximum severity			
Mild	4 (50.0)	13 (56.5)	17 (54.8)
Moderate	4 (50.0)	10 (43.5)	14 (45.2)
Severe	0	0	0
Life-threatening	0	0	0
Death	0	0	0
Missing	0	0	0
Subjects with AEs leading to study drug discontinuation	0	1 (4.3)	1 (3.2)
Subjects with AEs leading to study drug interruption	0	3 (13.0)	3 (9.7)
Subjects with Grade 3/4/5 AEs	0	0	0
Subjects with related AEs[a]	4 (50.0)	12 (52.2)	16 (51.6)
Subjects with SAEs	0	2 (8.7)	2 (6.5)
Subjects with related SAEs[a]	0	0	0
Subjects with AEs leading to death	0	0	0

Source: Ad hoc Table 14.3.1.1.1

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

Notes: AEs were coded using MedDRA 26.0. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and % 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 (serious) AEs, AEs with relationship of related, possibly related, and missing were counted.

Table 39: AEs Occurring in ≥5% of Patient in Any Treatment Group by PT (Safety Set, Study 124)

PT	Placebo N = 8 n (%)	ELX/TEZ/IVA N = 23 n (%)
Subjects with any AEs	8 (100.0)	23 (100.0)
Cough	2 (25.0)	7 (30.4)
Headache	1 (12.5)	6 (26.1)
Nasopharyngitis	2 (25.0)	6 (26.1)
Pyrexia	4 (50.0)	6 (26.1)
Vomiting	3 (37.5)	6 (26.1)
Rash	0	5 (21.7)
Rhinorrhoea	1 (12.5)	5 (21.7)
Diarrhoea	1 (12.5)	4 (17.4)
Infective PEx of CF	2 (25.0)	4 (17.4)
Abdominal pain	3 (37.5)	3 (13.0)
Oropharyngeal pain	1 (12.5)	3 (13.0)
Urticaria	0	3 (13.0)
Blood creatine phosphokinase increased	1 (12.5)	2 (8.7)
Eye pain	0	2 (8.7)
Gastroenteritis	1 (12.5)	2 (8.7)
Nausea	0	2 (8.7)
Otitis externa	0	2 (8.7)
Upper respiratory tract infection	1 (12.5)	2 (8.7)
Ear pain	2 (25.0)	1 (4.3)
Nasal congestion	2 (25.0)	1 (4.3)
Respiratory tract infection	1 (12.5)	1 (4.3)
Rhinitis	1 (12.5)	1 (4.3)
Bacterial disease carrier	1 (12.5)	0
Dizziness	1 (12.5)	0
Epistaxis	2 (25.0)	0
Fungal disease carrier	1 (12.5)	0
Odynophagia	1 (12.5)	0
Oral fungal infection	1 (12.5)	0
Rhinitis allergic	1 (12.5)	0
Toothache	1 (12.5)	0

Source: Ad hoc Table 14.3.1.3.1
AE: adverse event; CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor
Notes: AEs were coded using MedDRA version 26.0. A subject with multiple events within a category (Any or PT) was counted only once in that category. Table is sorted in descending order of frequency of the ELX/TEZ/IVA column by PT.

The AEs reported in subjects 65 years of age and older were mostly consistent with common manifestations or illnesses associated with CF disease or expected ageing. No firm conclusions can be drawn regarding safety in patients aged 65 or older due to the limited number of patients included.

Regarding paediatric patients aged 6-11 years of age, no firm conclusions could be drawn either due to the limited number of patients included. The safety profile of ELX/TEZ/IVA in these subjects was generally consistent with previous studies in a similar age population. No additional risk minimisation is considered warranted at present based on available safety data

Safety in people with CF and the *N1303K* mutation (Solomon et al.)

For CF patients with at least one *N1303K* mutation, safety assessments were conducted in Solomon et al., including clinical laboratory assessments, ECGs, and AE assessment. The authors reported that AEs were consistent with prior studies, with the most common AEs including headache, GI disturbance, and change

in sputum. The authors also reported no laboratory or ECG abnormalities attributed to study drug, and 1 subject who was hospitalised for pneumonia and PEx of CF at Day 16 of the Washout Period.[20]

In addition, Burgel et al. concluded that safety data in the 84 people with CF and ELX/TEZ/IVA responsive mutations enrolled in the French Compassionate Program (including those with an N1303K mutation) were generally consistent with the well-established safety profile of ELX/TEZ/IVA.[21]

Safety related to drug-drug interactions and other interactions

No new information is available.

Discontinuation due to adverse events

Five (2.4%) subjects in the ELX/TEZ/IVA group discontinued study drug due to AEs (1 subject due to liver function test elevations, 1 subject due to AEs of lung adenocarcinoma and pneumonia, 1 subject due to diarrhoea, 1 subject due to hepatic cytolysis, and 1 subject due to rash maculopapular). No subjects in the placebo group discontinued study drug due to an AE.

The majority of subjects discontinued study drug due to AEs that were moderate in intensity and non-serious. These events were generally consistent with prior experience.

Table 40: Study 124 TEAEs leading to treatment discontinuation by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Subjects with TEAEs leading to treatment discontinuation	0	5 (2.4)
Gastrointestinal disorders	0	1 (0.5)
Diarrhoea	0	1 (0.5)
Hepatobiliary disorders	0	1 (0.5)
Hepatic cytolysis	0	1 (0.5)
Infections and infestations	0	1 (0.5)
Pneumonia	0	1 (0.5)
Investigations	0	1 (0.5)
Alanine aminotransferase increased	0	1 (0.5)
Aspartate aminotransferase increased	0	1 (0.5)
Blood creatine phosphokinase increased	0	1 (0.5)
Gamma-glutamyltransferase increased	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5)
Lung adenocarcinoma	0	1 (0.5)
Skin and subcutaneous tissue disorders	0	1 (0.5)
Rash maculo-papular	0	1 (0.5)

- MedDRA version 26.0.
- 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.

[20] Solomon G. Oral Presentation: Interim results of an open-label trial to evaluate ETI in individuals with cystic fibrosis and an N1303K mutation who are not eligible for modulator treatment. Presented at: 2023 North American Cystic Fibrosis Conference, 03 November 2023, Phoenix, AZ.
[21] Burgel PR, Sermet-Gaudelus I, Durieu I, Kanaan R, Macey J, Grenet D, et al. The French Compassionate Program of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del CFTR variant. Eur Respir J. 2023;Online Ahead of Print:1-27.

Adverse Events Leading to Interruption of Study Drug

Study drug interruptions due to AEs were reported in 25 (12.2%) subjects in the ELX/TEZ/IVA group and 1 (1.0%) subject in the placebo group (**Table *41***). AEs leading to treatment interruption that occurred in >1 subject in the ELX/TEZ/IVA group were rash (14 [6.8%] subjects), alanine transaminase (ALT) increased (3 [1.5%] subjects), aspartate transaminase (AST) increased (3 [1.5%] subjects), and gamma-glutamyl transferase (GGT) increased (3 [1.5%] subjects).

The majority of AEs leading to study drug interruption were mild or moderate in intensity and non-serious.

Table 41: Study 124 TEAEs leading to treatment interruption by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Placebo N = 102 n (%)	ELX/TEZ/IVA N = 205 n (%)
Subjects with TEAEs leading to treatment interruption	1 (1.0)	25 (12.2)
Skin and subcutaneous tissue disorders	0	15 (7.3)
Rash	0	14 (6.8)
Urticaria	0	1 (0.5)
Gastrointestinal disorders	1 (1.0)	4 (2.0)
Abdominal pain	0	1 (0.5)
Diarrhoea	0	1 (0.5)
Lip swelling	0	1 (0.5)
Pancreatitis	0	1 (0.5)
Dyspepsia	1 (1.0)	0
Investigations	0	3 (1.5)
Alanine aminotransferase increased	0	3 (1.5)
Aspartate aminotransferase increased	0	3 (1.5)
Gamma-glutamyltransferase increased	0	3 (1.5)
Blood bilirubin increased	0	1 (0.5)
Blood creatine phosphokinase increased	0	1 (0.5)
Infections and infestations	0	2 (1.0)
Hepatitis viral	0	1 (0.5)
Sinusitis	0	1 (0.5)
Eye disorders	0	1 (0.5)
Swelling of eyelid	0	1 (0.5)
Musculoskeletal and connective tissue disorders	0	1 (0.5)
Exertional rhabdomyolysis	0	1 (0.5)
Reproductive system and breast disorders	0	1 (0.5)
Testicular pain	0	1 (0.5)

- MedDRA version 26.0.
- 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.

Post marketing experience

Since the International Birth Date of 21 October 2019, it is estimated that 67,637 patients (representing 107,050 person-years) have been treated with ELX/TEZ/IVA cumulatively as of 20 April 2023. Post-marketing reports of liver injury and depression have been reported and the ELX/TEZ/IVA labels have been updated accordingly, where required..

2.5.1. Discussion on clinical safety

ELX/TEZ/IVA in combination with IVA is generally safe and well tolerated in CF patients ≥2 years of age, based on data from more than 3,328 subjects treated with ELX/TEZ/IVA in combination with IVA for varying durations up to 4 years. With the current Study 124, another 205 subjects 6 years of age and older received at least 1 dose of study drug.

The mean exposure in Study 124 was 23.3 weeks in the ELX/TEZ/IVA group.

Although the proportion of subjects with at least 1 adverse event (AE) was high (94.5%), most subjects had AEs that were mild or moderate in severity. Fifteen (7.3) subjects had severe AEs, while there was 1 non-related event of death.

The most common AEs (occurring in ≥5% of subjects) were generally consistent with common manifestations of CF disease or with common illnesses in CF subjects 6 years of age and older. Most commonly observed AE nasopharyngitis, headache, cough, infective pulmonary exacerbation (PEx) of CF, pyrexia, and diarrhoea in both groups, while rash was also observed in 22% of the subjects in the ELX/TEZ/IVA group. It was further noticed that the incidence of influenza events was also notably higher in the ELX/TEZ/IVA group compared to the placebo group. This ties in with the fact that susceptibility for influenza virus infections is already identified as an important identified risk of ELX/TEZ/IVA. Therefore, no further update is deemed necessary.

A higher proportion of subjects had related AEs in the ELX/TEZ/IVA group compared to the placebo group, mainly cause by the differences in the SOC Skin and subcutaneous tissue disorders (rash) and the SOC Psychiatric disorders (insomnia). Rash is a well-known ADR of ELX/TEZ/IVA, while from the SOC Psychiatric disorders, only depression is included in the SmPC currently. However as psychiatric events will be reviewed in the upcoming PSURs, this is not further pursued currently.

Overall, the number of SAEs was low, while the proportion of subjects with a SAEs was lower in in the ELX/TEZ/IVA group compared to the placebo group. SAEs that occurred in ≥2 subjects in the ELX/TEZ/IVA group included infective PEx of CF and bronchopulmonary aspergillosis allergic and infective PEx of CF in the placebo group. Only two SAE (subileus and rash maculo-papular) in the ELX/TEZ/IVA were assessed as related to study drug.

Discontinuation was quite low, as only five (2.4%) subjects in the ELX/TEZ/IVA group and no subjects in the placebo group discontinued study drug. Also, the number of AEs leading to interruption of study drug was acceptable (12.2% in the ELX/TEZ/IVA group and 1% in the placebo group). Interruption occurred because of as rash, ALT increased, AST increased, and GGT increased, knows causes for interruption of treatment with ELX/TEZ/IVA.

Elevated transaminase events were considered an AE of special interest (AESI) and occurred in 8 (3.9%) subjects in the ELX/TEZ/IVA group. None elevated transaminase events were serious. ALT or AST >3 and >5 × ULN and >8 × ULN occurred in 13 (6.3%), 4 (2.0%), and 4 (2.0%) subjects in the ELX/TEZ/IVA group, respectively. No subjects had ALT or AST >3 × ULN with total bilirubin elevation >2 × ULN. Overall, AESIs of transaminase events in Study 124 were consistent with prior experience. Four hepatic AEs were reported of which 2 were considered possibly treatment related (hepatic cytolysis with moderate severity and CF hepatic disease with mild severity). An adequate warning and recommendation for regular assessment is already included in the SmPC.

Rash was also considered an AESI. Rash occurred in 55 (26.8%) subjects in the ELX/TEZ/IVA group and 3 (2.9%) subjects in the placebo group. One (0.5%) subject in the ELX/TEZ/IVA group had a serious rash event that was considered related to study drug and led to treatment discontinuation. More female subjects who use hormonal therapy (40%) had rash compared to female subjects who did not use

hormonal therapy (27.3%). A relation with hormonal therapy cannot be excluded; this is already included in section 4.4 of the SmPC. Thus, no further action is required.

There were no clinically relevant trends in other laboratory values except for creatinine kinase (CK). AEs of blood creatine phosphokinase increased occurred, i.e. in 3.4% subjects in the ELX/TEZ/IVA group and 2.9% subjects in the placebo group, while in the threshold table more subjects in the ELX/TEZ/IVA group had elevation of CK. In the ELX/TEZ/IVA group, 2 subjects had an AE of rhabdomyolysis of which 1 led to treatment interruption. They presented with blood creatine phosphokinase elevation but did not have features consistent with rhabdomyolysis (e.g., kidney involvement, myoglobinuria) and was attributed to heavy exercise in the prior 72 hours.

There were no clinically relevant trends, vital signs, ECGs, or pulse oximetry.

Previous studies of ELX/TEZ/IVA have shown that the safety profile is generally similar across subgroups of patients, including age, sex, ppFEV1, and geographic regions and subjects with different genotypes. In Study 124, the AEs reported for subjects 65 years of age and older were mostly consistent with common manifestations or illnesses associated with CF disease or expected ageing. However, the number of elderly subjects was too low (n=5 treated with ELX/TEZ/IVA) to draw firm conclusions.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

In Study 124, 31 patients participated aged 6 through 11 years (inclusive), of whom 23 received ELX/TEZ/IVA. There were no Grade 3/4/5 AEs and 1 patient discontinued treatment due to an AE of diarrhoea of moderate severity. In total 2 SAEs were reported for the ELX/TEZ/IVA arm vs. none in the placebo arm, i.e. (entero)viral hepatitis and infective PEx of CF. Study drug dosing was interrupted in the first and not changed in the latter event. Both events resolved and study drug was resumed/continued. Due to the small sample size for the subgroup of subjects 6 through 11 years of age, safety results should be interpreted with caution, although it is reassuring that previous studies with ELX/TEZ/IVA did not indicate differences in the safety profile of children, adolescents, and adults. No additional risk minimisation is considered warranted at present for patients aged 6 through 11 years of age.

2.5.2. Conclusions on clinical safety

ELX/TEZ/IVA and IVA were generally safe and well tolerated for 24 weeks of treatment in subjects 6 years of age and older, as demonstrated by the low number of severe AE, (related) SAEs and low number of discontinuations due to an AE. No new safety concerns were identified as the data was generally consistent with prior experience.

2.5.3. PSUR cycle

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.

3. Risk management plan

The WSA submitted/was requested to submit an updated RMP version with this application. The main proposed RMP changes were the following:

- To support the extension of indication of Kaftrio, relevant sections of the RMP were updated based on the final data from the Phase 3 Study VX21-445-124 in CF subjects with a non-F508del ELX/TEZ/IVA-responsive CFTR mutation.
- The Pharmacovigilance Plan of the RMP was updated to include Study VX21 445 125 for evaluation of the long-term safety and efficacy of ELX/TEZ/IVA treatment in CF subjects with non-F508del CFTR genotypes
- Consolidation of changes from RMP Version 7.3 (completion of 96 weeks of treatment in Study 107) and RMP Version 8.1 (2 to <6 years indication expansion)
- The clinical trial and post-authorisation exposures were updated

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.0 for Kaftrio is acceptable and version 16.0 for Kalydeco is acceptable.

3.1. Safety concerns

Kaftrio Table SVIII.1: Summary of the Safety Concerns

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

Kalydeco EU-RMP v16.0

- **Summary of safety concerns**

Important identified risks	***None***
Important potential risks	• Hepatotoxicity • Cataract
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

3.2. Pharmacovigilance plan

Kaftrio

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
Not applicable				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
Not applicable				
Category 3 – Required additional PV activities (by the competent authority)				
PASS Ongoing	Evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting	• Susceptibility for influenza virus infections • Hepatotoxicity • Use in patients with moderate or severe hepatic impairment • Use in pregnant women • Long-term safety • Use in children aged 2 to 11 years	Annual Reports Final Report	31 December 2021/2022/ 2023/2024 31 December 2025
Open-label extension study (Study 112) Ongoing	Evaluate the long-term safety, tolerability, efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in CF subjects 2 years of age and older	• Susceptibility for influenza virus infections • Hepatotoxicity • Cataract • Long-term safety • Use in children aged 2 to 11 years	Final Report	June 2025
Open-label extension study (Study 125) Ongoing	Evaluate the long-term safety, tolerability, efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in CF subjects without *F508del* mutation	• Susceptibility for influenza virus infections • Hepatotoxicity • Cataract • Long-term safety • Use in children aged 2 to 11 years	Final Report	31 December 2025

CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; *F508del*: an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein; MA: market authorisation; PASS: post-authorisation safety study; PD: pharmacodynamics; PV: pharmacovigilance; Study 112: VX20-445-112; Study 125: VX21-445-125

- **Kalydeco summary table**

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)				
None				
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)				
None				
Category 3 – Required additional PV activities (by the competent authority)				

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study 126 Ongoing	<u>IVA Arm</u> In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation: • To evaluate the safety of long-term IVA treatment • To evaluate the PD of long-term IVA treatment • To evaluate the efficacy of long-term IVA treatment <u>Observational Arm</u> To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation	• Hepatotoxicity • Cataract • Indicated use in children aged <24 months old at initiation	Final Report	December 2023

CF: cystic fibrosis; IVA: ivacaftor; MA: market authorisation; PD: pharmacodynamics; PV: pharmacovigilance

Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

PART IV Plans for Post-authorisation Efficacy Studies -Kaftrio

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the MA				
Post-Authorisation Efficacy Study (PAES) (Study Number 131) Planned	To evaluate disease progression among children with CF who are heterozygous for *F508del* and are aged 2 through 5 years at the time of ELX/TEZ/IVA initiation	Long-term efficacy among children with CF who are heterozygous for *F508del* and aged 2 through 5 years at the time of ELX/TEZ/IVA initiation	Protocol Submission	30 June 2024
			Final Study Report	31 December 2029
Efficacy studies which are Specific Obligations in the context of a conditional MA or a MA under exceptional circumstances				
None				

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator gene; MA: marketing authorisation; PAES: Post-Authorisation Efficacy Study

3.3. Risk minimisation measures

Kaftrio

Table 42 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Susceptibility for influenza virus infections	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 112) (Final Report: June 2025) • Open-label extension study (Study 125) (Final Report: 31 December 2025)
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:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 112) (Final Report: June 2025) • Open-label extension study (Study 125) (Final Report: 31 December 2025)
Cataract	**Routine risk minimisation measures:** SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided. PL Section 2 PL Section 2 where expectations for eye examinations are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 112) (Final Report: June 2025) • Open-label extension study (Study 125) (Final Report: 31 December 2025)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and lactating women	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3 SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding. PL Section 2 PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up questionnaire **Additional PV activities:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Long-term safety	**Routine risk minimisation measures:** SmPC Section 4.8 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 112) (Final Report: June 2025) • Open-label extension study (Study 125) (Final Report: 31 December 2025)
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 2 to 11 years	**Routine risk minimisation measure:** SmPC Sections 4.1, 4.2, and 4.4 PL Sections 1 and 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 112) (Final Report: June 2025) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025) • Open-label extension study (Study 125) (Final Report: 31 December 2025)

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

Kalydeco

Table 43 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. 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:** Study 126
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 Prescription only	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126

	Additional risk minimisation measures: None	
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up form **Additional PV activities:** None
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 Prescription only **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126

PL: Patient Leaflet; SmPC: Summary of Product Characteristics

Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

3.4. Pharmacovigilance

3.4.1. Pharmacovigilance system

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

4. Changes to the Product Information

As a consequence of this extension of indication, sections 4.1, 4.2, 4,4, 4.8 and 5.1 of the SmPC of Kaftrio and Kalydeco are being updated. Additional minor linguistic changes are introduced (section 5.2 of SmPCs).

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information of both medicinal products.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons: this update does not impact the readability of the package leaflet, and that further readability testing is not considered necessary for both Kaftrio and Kalydeco. This is agreed by CHMP.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality. 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, that regulates chloride transport. A defect in the CFTR protein results in the multisystem pathology associated with CF.

CF-causing mutations are divided into minimal function (MF) and residual function (RF) mutations based on the extent of loss of chloride transport caused by the mutation. MF/MF genotypes are usually associated with severe CF disease with signs and symptoms presenting at early age. MF/RF or RF/RF genotypes may result in milder forms of disease with signs and symptoms presenting later in life.

Of the approximately 54,000 CF patients in Europe, there are approximately 8,500 people with CF without an *F508del* mutation. People with CF who do not carry at least one *F508del* mutation are rare and have CFTR mutations that are individually rare.

The current application refers to the smaller subset of CF patients that do not harbour an F508del mutation (20%). This population harbours multiple variants of CFTR-mutations. Individually these mutations are rare.

The current application is based on an extension of indication in non F 508 del mutations CF patients based on clinical data and /or in vitro data. The in vitro data refers to those CFTR mutations that show a positive response in the in vitro FRT assay by showing an increase of > 10% over baseline.

5.1.2. Available therapies and unmet medical need

Existing CF treatments can be broadly classified in 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) that target the underlying cause of the disease.

Modulators such as Kaftrio have gained an important place in the treatment of CF. They have been shown to have systemic benefit and to modify the course of CF disease with long-term treatment for individuals by improving lung function and quality of life. However, they are indicated for a limited population, i.e., people with CF who harbour an *F508del* mutation. Non-*F508del* CFTR mutations are not currently indicated for treatment with CFTR modulators and the patients with these mutations must continue to rely on adjunctive treatments and symptomatic therapies to manage their CF disease.

For these patients without *F508del* CFTR mutations, there is an unmet medical need.

5.1.3. Main clinical studies

To establish benefit/risk in patients with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)-responsive, non-*F508del* CFTR mutations, the following clinical data have been submitted:

1. Efficacy and safety data from pivotal Study 124: a randomised, double-blind, placebo-controlled trial conducted in CF patients aged ≥ 6 years without an *F508del* mutation and who harboured at least one of the following 18 CFTR mutations: *2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077, M1101K*.
   These selected mutations are the most frequently reported CF mutations within the CF population that show a response to ELX/TEZ/IVA in the FRT assay or to Symkevy in heterozygotic *F508del* patients (splice mutations).
2. Efficacy data from Study 125: the open-label extension of Study 124. This study provided additional 4-week efficacy data of subjects initially randomised to placebo and subjects already treated with ELX/TEZ/IVA. This study is ongoing.
3. Real World Evidence (RWE) data obtained in Study CFD-016 from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) included 82/177 ELX/TEZ/IVA-responsive non-*F508del* CFTR mutations. The observation period was 21 Oct 2019 to 01 Dec 2022.
4. Bibliographical data from 3 independent investigator-initiated studies were provided to support the application for the *N1303K* mutation, a relatively common mutation that is not responsive in the FRT assay.
5. Bibliographical data referring to Real World Data (RWD) obtained in the Expanded French Compassionate program (FCP) published by Burgel et al. in Lancet Respir Med 2024; 12: 888–900.

The Expanded FCP was open to a non-F CF population regardless the presence of an FRT responsive mutation. This trial likely included the most prevalent non-F CFTR mutations in France, while it also collected data for those CFTR mutations that failed to show a response in the FRT assay.

6. Non-clinical data from the FRT assay (MAH own test)

On day 0, Results of study P289 were provided showing the in vitro responsiveness of 177 mutations

At the end of the procedure, results of study U032 were provided, showing the in vitro responsiveness of an additional 337 mutations

5.2. Favourable effects

Study 124

The pivotal Study 124 met its primary endpoint and was supported with the secondary endpoints:

- ELX/TEZ/IVA showed superiority compared to placebo in the absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) through Week 24, i.e. LS Mean = 9.2% (95% CI: 7.2, 11.3), *P*<0.0001.
- The secondary outcomes showed an LS mean treatment difference in the absolute change of sweat chloride (SwCl) from baseline through Week 24 of -28.3 mmol/L (95% CI: -31.1, -24.5), the Cystic Fibrosis Questionnaire - Revised Respiratory Domain (CFQ-R RD) score of 19.5 points (95% CI: 15.5, 23.5), Body Mass Index (BMI) 0.47 kg/m^2 (0.24, 0.69) and a reduction of pulmonary exacerbation (PEx) rate of 0.28 (95% CI: 0.15, 0.51) (all *P*<0.0001).

Consistent results for the ppFEV1, SwCl and CFR-Q were observed in the subgroup analyses according to age (<18, ≥18 years), ppFEV1 at baseline (<70%, ≥70%), sex and the ad hoc subgroup analyses according to CFTR mutation with ≥5 subjects.

Study 125

The additionally provided 4-week efficacy data support the efficacy results of Study 124.

CFD-016 (RWE)

Results were provided for a cohort of 422 non-*F508del* patients in which 82/182 eligible mutations were represented. The mean change from baseline in ppFEV1 through the follow-up period was 4.53 percentage points (95% CI: 3.50, 5.56). Improvements were also observed in weight and BMI. The number of PEx declined by 53% (95% CI: 42, 62).

Expanded French Compassionate Program

Results were provided for a cohort of 479 non-*F508del* patients of French CF centres. The overall improvement in ppFEV1 was ~7.5%.

The overall included population showed a clinical response in 61% of those treated with E/T/I. For pwCF harbouring an FDA approved (FRT responsive) mutation, the response rate was 96%, while the complementary group with a non-FDA approved mutation showed a response rate of 50%.

Bibliographical data on the *N1303K* mutation

The collected data is obtained for ≥ 72 treated N1303K patients including homozygous N1303K and N1303K/Stopcodon patients. The patients showed a response to ppFEV1 (median reported improvement ranging from 6-17 % ppFEV1) after treatment.
The clinical results are supported with additional references showing an in vitro response for the N1303K mutation using human bronchial epithelial nasal cells or rectal organoids.

FRT Assay

The FRT assay shows a high positive predictive value and sensitivity under different assumptions; in the clinical package the FRT assay had a sensitivity 90% of and a positive predictive value of 100%, for those

variants with ≥ 5 patients in the RCT.
In the FCP, the sensitivity ranged from 75 to 89%% and the positive predictive value from 63% to 100% taking into consideration the responsiveness of the second allele.

5.3. Uncertainties and limitations about favourable effects

Study 124

Study 124 was not open to all E/T/I responsive CFTR mutation but restricted the inclusion to the 18 most frequently reported ELX/TEZ/IVA responsive non-*F508del* mutations (FRT-responsive or non-canonical splice mutations).

The selected ELX/TEZ/IVA-responsive mutations were both MF and RF mutations. Subgroup analysis is missing according to the stratification factor for CFTR classification (MF/MF versus MF/RF and RF/RF).

No data has been collected for children aged 2-5 years.

CFD-016 (RWD)

The US CFFPR registry did not provide data for all applied CFTR mutations (182 non F508 del mutations) as only 82/182 ELX/TEZ/IVA responsive mutations were included. The subgroup analyses according to CFTR mutation of 20 CFTR mutations with ≥5 patients with available data show variable results as the CFFPR data standards do not allow reporting of health characteristics of small patient subgroups (i.e. < 5 patients) due to patient privacy concerns.

Expanded French Compassionate program (RWD)

The results are obtained from bibliographical data obtained in a single arm trial. The clinical responsiveness was determined by the Central committee on the totality of clinical data, and not restricted to improvement in ppFEV1 (such as in the clinical trials).

Bibliographical data on the *N1303K* mutation

The supportive bibliographical data is obtained from single arm trials, and the results can regress to the mean.

The observed discrepancy in clinical response in ppFEV1 and SwCl compared with the negative results on FRT assay is not understood.

The FRT assay

The in vitro data is supported by the Fisher Rat Thyroid (FRT) assay, only. This assay has not been subject to an EU qualification procedure and is considered by CHMP not validated based on insufficient data provided during the procedure despite CHMP requests. It is concluded that, a positive result in the FRT assay could be seen as indicative for providing a response upon clinical treatment for a tested CFTR variant. However, a negative result in the FRT is not regarded indicative for treatment failure in patient carrying that tested CFTR mutant. Therefore, it is emphasized that patients carrying mutants not tested (positive) in the FRT assay should not be excluded from a trial-of-therapy as a negative response in the FRT assay can be still associated with a positive clinical outcome (e.g. N1303K, R334W, R1066C mutations).

The results of the FRT assay are provided solely by the Applicant. No results obtained by an independent party are provided.

The FRT assay is a transformed cell line, so it may have altered characteristics compared with human epithelial cells. As mentioned in the Ad-Hoc Expert meeting, the FRT assay measures the response of one CFTR mutation. It is therefore, considered an artificial model and not a replication of the complexity of

human tissue where CFTR activity is influenced by local factors (e.g. immune response) or modulator genes. As a result, the correlation between FRT response and clinical response for a specific CFTR mutation is hard to predict. This is further complicated by pwCF harbouring the same mutation showing a high inter-patient variability in response,

The threshold for the 10% percentage improvement over normal baseline is rather conservative, CFTR variants showing a lower response may respond clinically (e.g. N1303K, R334W, R1066C that show negative response to FRT test).

The attribution of clinical responsiveness to a specific CFTR variant is difficult as the clinical response can be attributed to both alleles (if responsive), the non-F CF population is small and the non-CFTR mutations are individually rare.

In the FUP, the presence of the second allele was considered when determining the responsiveness of a CFTR variant. However, the attribution of responsiveness is difficult as only for a minority of variants (~20%) an unequivocal conclusion could be made.

The discriminatory statistics of the FRT assay are based on the collection of CFTR variants with available FRT data and sufficient clinical data; however, the specific CFTR variant subgroups were usually small.

The discriminatory analyses of the FRT assay based on the clinical package used the provided thresholds for clinical response in ppFEV1 ≥0% and SwCl ≥10 mmol/L. These are the absolute minimum for supporting a clinical benefit.

The FRT assay cannot evaluate all CFTR variants.

5.1. Unfavourable effects

The proportion of subjects with at least 1 adverse event (AE) was high (94.5%)

The most common AEs were nasopharyngitis, headache, cough, infective pulmonary exacerbation (PEx) of CF, pyrexia, and diarrhoea, generally comparable in both groups. However, there was a clear difference in rash events, i.e., 22% in the ELX/TEZ/IVA and 1.0% in the placebo group.

Related AEs were higher in the ELX/TEZ/IVA group. The difference is mainly explained by the differences in the SOC Skin and subcutaneous tissue disorders (rash), the SOC Investigations (elevated transaminase) and the SOC Psychiatric disorders (insomnia).

5.2. Uncertainties and limitations about unfavourable effects

The safety in elderly subjects is limited (n=5) as life expectation in CF is still limited. Safety might be different in elderly people.

Although safety in children 6 through 12 years in previous studies was similar to adults and adolescents, safety data in this group is limited in the pivotal trial (n=31). No firm conclusions can be drawn based on these data, but it is reassuring that no new safety signal was observed for included patients aged 6 through 11 years.

5.3. Effects Table

Table 44: Effects Table Extension of indication for non-F058del CF patients with ELX/TEZ/IVA response CFTR mutations aged ≥ 2 years (data cut-off: 05 July 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			ELX/TEZ/IVA N=205	Placebo N=102		
Favourable Effects						
Non-*F508del* CF patients with an in vitro responsive ELX/TEZ/IVA mutation						
ppFEV1	Change 0-24 wks. LSM (95% CI)	%	8.9 (7.7, 10.0)	-0.4 (-2.0, 1.3)	LSM difference 9.2 (7.2, 11.3), *p* <0.0001 Clinically relevant / Based on subset of preselected subset of 18 ELX/TEZ/IVA-responsive CFTR mutations	Study 124
sweat chloride	Change 0-24 wks. LSM (95% CI)	mmol/L	-27.8 (-30.0, -25.6)	0.5 (-2.6, 3.6)	LSM difference -28.3 (-32,1, -24.5), *p* <0.0001	Study 124
Non-*F508del* CF patients with *N1303K* mutation						
ppFEV1	Mean change after 4-8 weeks of treatment	%		NA	N=72 patients, Mean change in FEV1 varies from 7 to 18 % in The *N1303K* mutation is not considered ELX/TEZ/IVA-responsive based on the *in vitro* FRT assay	Bibliographical data only Single arm trial Burgel et all 2024 Solomon et al 2024 Canan et al 2024 Kaftrio PASS Ad hoc subgroup study 124
sweat chloride	Mean change after 4-8 weeks of treatment	mmol/L		NA	Mean change varies from -0.1 to -9.0 mmol/L No change in largest study (n = 20)	
Unfavourable Effects						
rash	Percentage	%	22.0	1.0		Study 124
ALT elevated	Percentage	%	3.9	0.0		Study 124
AST elevated	Percentage	%	3.9	0.0		Study 124
influenza	Percentage	%	8.8	2.0		Study 124

Abbreviations: LSM: least squares mean; ppFEV1: percent predicted forced expiratory volume in 1 second; CFQ-R RD: Cystic Fibrosis Questionnaire - Revised Respiratory Domain; PEx: pulmonary exacerbation; BMI: body mass index; ALT: alanine transaminase; AST: aspartate transaminase

5.4. Benefit-risk assessment and discussion

5.4.1. Importance of favourable and unfavourable effects

Kaftrio and Kalydeco are effective medicines in combination which gained its first approval based on the most prevalent genetic mutation: the F508del. The F508del mutation is present in 80% of pwCF. Efficacy has been demonstrated in various RCTs showing robust and consistent improvement in ppFEV1 over placebo or Symkevi (F/F) populations. Modulator therapy, like Kaftrio, has been demonstrated to be a transformative advancement in the treatment of pwCF with at least one F508del mutation. Therefore, there is an unmet medical need for modulator therapy in pwCF without F508del mutation.

The currently applied indication refers to the non-F CF population. This subgroup refers to 20% of pwCF. The non-F CF population is genetically very heterogenous, including >1800 CFTR variants. The non-F CF population can be divided in pwCF homozygous for class I mutations, who will not respond to modulator therapy. This concerns about 3 to 5% of pwCF.

This clinical package refers to the other subgroup of non-F pwCF who may harbour potentially responsive non-F CFTR variants. These non-F CFTR mutations are individually rare.
Kaftrio/Kalydeco can be considered a precision medicine, but due to the rarity of the non-F508del CFTR variants, it is hard to collect sufficient clinical data for each of these rare non-F CFTR variants that might potentially respond to Kaftrio/Kalydeco treatment.

The current application is based on clinical and in vitro data. The in vitro data comes from the FRT test, an EU non-qualified test. The FRT assay is essentially a single cell line that measures the response to treatment for a specific CFTR mutation. The correlation between the FRT response and clinical response is difficult to predict, as it is not a replication of the human tissue environment.

For instance, the N1303K, R334W and R1066C mutations did not show a positive response in the FRT assay. However, these mutations were determined as being a responsive CFTR variant in the FUP based on provided clinical data in ≥ 5 pwCF. Although the observed discrepancy in clinical response in ppFEV1 and SwCl is not understood, we consider that the overall evidence shows a relevant effect that is sufficient to include these mutations in section 5.1 of the SmPC.

The current clinical package includes clinical data from an RCT and OLE study in a non-F CF population, RWD from a US registry and bibliographical data from the expanded French Compassionate program. The RWD obtained by the US registry included FRT responsive mutations only. During the procedure, data became available from the expanded French compassionate program, an observational study that was open to an all-comers non-F CF population in France.

The efficacy and safety results of the placebo controlled RCT in the non-F population aligned with the obtained clinical results in the complementary F508del population and provided sufficient clinical evidence for at least 12 in vitro E/T/I responsive CFTR mutations. The results were supported with the data gathered in the OLE study, US registry and the FUP. Overall, these data show improvements in ppFEV1 ≥7.5% for the non-F CF population that currently has no access to modulator therapy. The cross-study comparison shows that this improvement is larger than observed with Orkambi (ppFEV1 ~3%) or Symkevi (ppFEV1 ~5%) that led to the approval of modulator therapy for the F/F population.

The clinical package provided no references showing the correlation between the in vitro FRT response and clinical response. Evaluation of the provided clinical data showed that a positive FRT response of a CFTR variant is indicative of a clinical response. However, clinical responses were also observed in CFTR mutations that were considered non-responsive based on FRT data.
The attribution of the clinical responsiveness to a specific CFTR variant is difficult, however, as the clinical response can be obtained from a responsive CFTR variant on both alleles. Moreover, the non-F CF group is small and the non-F mutations are individually rare, resulting in small subgroups, while previous data showed that the interpatient variability in response is large among pwCF harbouring the same mutations. Therefore, uncertainties still existed if the FRT assay could be used solely to identify in vitro CFTR mutations without sufficient clinical data to be included in the extension of the indication claimed by the MAH

The Experts of the AHEG consulted on 28 Nov 2024 considered that reliance on the in vitro FRT results without sufficient clinical data could be acceptable. Should the indication be granted they however expressed concerns that such indication be based on the FRT assay as the test is not being performed by an independent body nor used in the clinical routine.

Considering the high unmet medical need, the AHEG agreed that a "trial of therapy" could allow patients to receive treatment rather than excluding patients based on their genetic profile of rare mutations for which clinical response/in vitro response is not known. However, clinical responsiveness of a specific CFTR variant cannot be predicted, also acknowledging that there is a large interpersonal variability in clinical response among pwCF who respond to treatment. The experts considered that a potential clinical

response can be evaluated over time, and that criteria for responsiveness should be evaluated in a personalised manner.

A restricted indication based on CFTR variants with clinical and/or in vitro data as proposed by the MAH would exclude pwCF based on the rarity of their genetic profile, despite the high unmet medical need. The current package included the most prevalent non-F CFTR mutations. Therefore, it can be assumed that it would be hard to collect sufficient clinical data to support the inclusion of ultra rare non-F mutations, while it also needs to be considered that not all CFTR mutations can be tested in the FRT assay. The delay in access to therapy is worrisome and considered unnecessary, since these pwCF are monitored in specialised centres, and other ex vivo/in vitro tests are available to test if these pwCF could be responsive. Rare non-F CFTR mutations are also more likely to occur in ethnic minorities, which may exacerbate inequities for patients of other ethnicities in equity deserving groups. Further collection of additional supportive data would be considered difficult if not infeasible.

The applied subset of in vitro FRT responsive CFTR mutations is a heterogenous group. Because of the large variability of the applied non-F CFTR mutations, the included non-F CF population will have a variable phenotype, ranging from mild to very severe CF. The clinical relevance of the observed improvements might differ for these different phenotypes. In conclusion taking the overall evidence into account, the CHMP considered that B/R could be extended to all CF patients, while excluding patients with homozygous class I mutations (section 4.1) which are non-responsive to CF modulator therapy.

Additional comments in section 4.2, 4.4 and 5.1. state that pwCF not harbouring one of the CFTR variants mentioned in section 5.1 could receive treatment under close supervision of the treating physician.

The list of mutations responsive clinically and with *in vitro* data is provided in section 5.1 of the SmPC.

The CHMP considered necessary to receive regular yearly update on the FRT negative and positive data collected post marketing as mutations are being tested. The MAH agreed to this commitment and submitted a letter of undertaking.

Safety

ELX/TEZ/IVA is generally safe and well tolerated in CF patients ≥2 years of age, based on data from more than 3,328 subjects treated with ELX/TEZ/IVA for varying durations up to 4 years. In study 124, and 125 safety was generally consistent with prior experience. No new safety concerns were identified.

Most important AEs such as hepatic events, rash and gastrointestinal disorders are manageable. Recommendations for regular assessments of transaminases are included in the SmPC for risk minimisation.

5.4.2. Balance of benefits and risks

Modulator therapy, like Kaftrio, has been demonstrated to be a transformative advancement in the treatment of pwCF harbouring at least one F508del mutation. There is an unmet medical need for pwCF without F508del mutation, as they are currently excluded from modulator therapy and no other treatments are available that can modify the course of the disease.

The obtained RCT data together with the supportive clinical data obtained by the OLE study, US registry and FUP of various CFTR variants, sufficiently supports the inclusion of non-F CFTR mutations in the indication of Kaftrio. The CFTR homozygous class I mutations patients will be non-responsive to modulator therapy and remain excluded from the indication.

5.4.3. Additional considerations on the benefit-risk balance

An Ad Hoc Experts Group (AHEG) meeting was convened on the 28 November 2024. The outcome of the AHEG is provided below.

The AHEG experts agreed that reliance on the in vitro FRT results without clinical data could be acceptable. Some experts mentioned that confirmation with clinical data should be generated after treatment. The experts raised concerns if the indication should be based on the FRT assay performed only by the company, while this test is not being performed by an independent body or in the clinical routine.

The AHEG experts agreed that a "trial of therapy" would be beneficial to allow patients to receive treatment rather than excluding patients with rare mutations for which clinical response/in vitro response is not known. They considered that a potential clinical response can be evaluated over time, and that criteria for responsiveness should be evaluated in a personalised manner.

The AHEG experts considered that, except for class I mutations, it is not possible to a priori identify CFTR mutations that will not be responsive to Kaftrio, also referring to the variability in the individual response among patients harbouring the same mutation.

Third party interventions

The CHMP received, during the assessment of this application, 11 correspondences from Cystic fibrosis associations and HCP associations and patients expressing the third parties' views about the efficacy and safety profile of Kaftrio, the French compassionate use, the FRT assay and the unmet medical need of CF patients.

The CHMP considered those interventions in the context of its assessment and concluded that the observations put forward by the third parties were already known by CHMP, and as such had no impact on the CHMP assessment or its conclusions.

5.5. Conclusions

The CHMP agreed to the extension of indication in the CF population for both Kalydeco and Kaftrio as detailed below (update in bold)

The overall B/R of Kaftrio (tablets/granules) is positive in the below indication:

Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 2 years and older **who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene**.

The overall B/R of Kalydeco (tablets/granules) is positive in the below indication:

Kalydeco tablets are indicated in a combination regimen with ivacaftor for the treatment in cystic fibrosis (CF) in patients aged 2 years and older **who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.**

In addition, the MAH should submit regular yearly updates of positive and negative results on the FRT test.

6. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
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 and IIIB

Extension of the indication for Kaftrio (ivacaftor/tezacaftor/elexacaftor) and Kalydeco (ivacaftor) based on study VX21-445-124, study VX21-445-125, study VX22-CFD-016 and results from a French compassionate use programme. The indication is extended to all patients with non-F *508* del mutations except homozygous patients who carry two class I mutations. In addition, the worksharing applicant took this opportunity to introduce editorial changes to the PI of Kalydeco and Kaftrio.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Kaftrio SmPC are updated and sections 4.1 4.2, 4.4, 4.8, 5.1 and 5.2 of the Kalydeco SmPC are updated. The Package Leaflet for both products is updated in accordance.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kaftrio is not similar to symkavi the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.