EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2021
EMA/206350/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kaftrio

International non-proprietary name: ivacaftor / tezacaftor / elexacaftor

Procedure No. EMEA/H/C/005269/0000

Note

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
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
COVID-19	coronavirus disease
CSR	clinical study report
Ctrough	predose concentration
ECG	electrocardiogram
ELX/TEZ/IVA	elexacaftor/tezacaftor/ivacaftor
EMA	European Medicines Agency
EU	European Union
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
FEV1	forced expiratory volume in 1 second
F/F	homozygous for F508del
F/MF	heterozygous for F508del and an MF mutation
G	gating
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GLI	Global Lung Function Initiative
IA	interim analysis
IVA	ivacaftor

LS	least squares
LUM/IVA	lumacaftor/ivacaftor
MAA	Marketing Authorization Application
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size
PD	pharmacodynamics
PEx	pulmonary exacerbation
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
q12h	every 12 hours
qd	once daily
R117H	CFTR missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
RD	respiratory domain
RF	residual function
SAEs	serious AEs
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SwCl	sweat chloride
TEZ	tezacaftor
TEZ/IVA	tezacaftor/ivacaftor
ULN	upper limit of normal
US	United States

Abbreviated Study Numbers

All clinical study numbers conducted with elexacaftor (ELX, as monotherapy or combination therapy) are abbreviated to the last 3 digits (e.g., Study VX17-445-102 is Study 102).

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 26 August 2020 an application for a variation.

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, IIIA and IIIB

Extension of indication of Kaftrio to patients with CF aged 12 years and older who have at least one F508del mutation in the CFTR gene, regardless of the second allele.
Efficacy data are summarized from Study 104, which was conducted in subjects heterozygous for F508del and a gating (G) or residual function (RF) mutation (F/G and F/RF genotypes).

As a consequence of this new indication and taking into account minor changes introduced, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Northern Ireland/UK.

The RMP is updated version 2.0

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Kaftrio, was designated as an orphan medicinal product EU/3/18/2116 on 14 December 2018. Kaftrio was designated as an orphan medicinal product in the following indication: Treatment of 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.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-002324-PIP01-17 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (EMEA-002324-PIP01-17) 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 MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Peter Kiely

Timetable	Actual dates
Submission date	26 August 2020
Start of procedure:	12 September 2020
CHMP Co-Rapporteur Assessment Report	6 November 2020
CHMP Rapporteur Assessment Report	5 November 2020
PRAC Rapporteur Assessment Report	10 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	23 February 2021
PRAC Rapporteur Assessment Report	23 February 2021
PRAC Outcome	11 March 2021
CHMP members comments	11 March 2021
Updated CHMP Rapporteur Assessment Report	18 March 2021
Opinion	25 March 2021

2. Scientific discussion

2.1. Introduction

Kaftrio is a CFTR modulator therapy that includes the active substances elexacaftor, tezacaftor and ivacaftor.

Kaftrio was approved in August 2020 in F/MF and F/F patient populations based on study results in F/MF (study 102) and F/F (study 103) CF patients. Long-term data from these F/MF and F/F populations were provided in study 105. The data of clinical studies 102, 103 and 105 indicated a large and maintained clinical benefit with ELX/TEZ/IVA in F/F and F/MF patients. Based on clinically relevant benefit and consistency of effects seen with ELX/TEZ/IVA in studies/subgroups, extrapolation to all patients with an F/MF genotype was considered acceptable (i.e. also with those MF mutations not tested in the clinical study).During the Initial MAA - Kaftrio CHMP AR (EMEA/H/C/005269/0000), the applicant initially applied for a broader indication (F/any indication). This broader indication was based on the idea that Kaftrio mainly acts through the *F508del* allele and thus all patients with an *F508del* allele could be included in the indication. While the effects in the F/MF population and all additionally provided information made it plausible that the ELX/TEZ/IVA mainly acts through the *F508del* allele and would also have resulted in a benefit in for example the F/RF and F/G population; the approval of the broad F/any indication was not supported as it was not possible to determine the added benefit of the triple combination over approved IVA and TEZ/IVA without a study in F/RF or F/G patients.

In the current procedure, data in the F/RF and F/G populations are provided (study 104) and the MAH applied again for the broad F/any indication:

> *"Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene."*

2.1.1. Problem statement

Disease or condition

Cystic Fibrosis (CF) 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 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 results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

F508del is the most common disease-causing mutation (84.7% of the individuals in the US and 81.1% of the individuals in Europe)[1,2]. With the proposed indication 'F/any', this would result in treatment possibility in the vast majority of the CF patients.

Epidemiology

CF affects approximately a total of 31,000 individuals in the United States and a total of 42.000 in the EU (excluding the data from Russia, Turkey and Israel)[3,4]. The incidence and prevalence of CF vary between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations. In Europe, the median age of all CF patients is 18.5 years (with youngest patient being diagnosed just after birth and the oldest patients being 88.4 years of age). Despite advances in treatment, the current median age of death in a patient with CF was approximately 31 years in 2018, and the future predicted median age of survival is approximately 47 years[1,2].

Aetiology and pathogenesis

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

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

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

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

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

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

Most of these mutations are not associated with CF disease or are very rare. Currently, the CFTR2 database (an online resource that provides clinical and non-clinical data about CF-associated CFTR

[1] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2019.

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

mutations) contains information on 412 of these identified mutations, with sufficient evidence to define 346 mutations as disease-causing.

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

The MAH uses slightly different definitions, especially when considering "minimal function" mutations.

- Gating mutations (G) result in a CFTR protein with a primary defect of low channel open probability compared to normal CFTR (comparable to Class III).
- Residual function (RF) mutations result in a more modest reduction in CFTR-mediated chloride transport than Class I mutations or minimal function mutations (comparable to Class IV).
- Minimal function (MF) mutations produce (1) no CFTR protein or (2) a CFTR protein that is not responsive to IVA and TEZ/IVA *in vitro*. (comparable to Class I)

For convenience, in this report, the definitions of the company will be used, and 4 different CF population will be described:

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

Clinical presentation, diagnosis

CF is diagnosed when both of the following criteria are met

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

  AND

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

Around 2 percent of patients lack one or more of the "CLASSIC" features. They may have milder clinical symptoms and/or normal to intermediate sweat chloride results. These patients can still be diagnosed with CF if they meet genetic or functional criteria[3].

Management

Existing treatments for CF can be broadly classified in 2 groups: (1) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics, mucolytics, pancreatic

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

enzyme replacement therapy) and (2) CFTR modulators (i.e., correctors and potentiators) which target the underlying cause of the disease. Concomitant administrations of these two groups are recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

(1) CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. These therapies are predominantly generic medicines 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 (tezacaftor and lumacaftor) facilitate the cellular processing and trafficking of CFTR to increase the quantity of CFTR at the cell surface. Potentiators (ivacaftor) increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance chloride transport. A combination of a corrector and a potentiator, should results in sufficient levels of CFTR at the surface, which is then enhanced for its gating function. Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA), Symkevi (tezacaftor/ivacaftor, TEZ/IVA) and Kaftrio (elexacaftor/tezacaftor/ivacaftor, ELX/TEZ/IVA) are CFTR modulators approved for CF patients with specific mutations. Not all CFTR genotypes are indicated for approved modulator therapies, and not all patients are able to tolerate the therapy.

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

2.1.2. About the product

Kaftrio (elexacaftor/tezacaftor/ivacaftor) 100 mg/50 mg/75 mg is a fixed-dose combination medicinal product for oral administration in tablet form.

Kaftrio belongs to the pharmacotherapeutic group of other respiratory system products with ATC code R07AX32.

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

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

- Morning dose: 2 fixed-dose combinations (FDC) tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg), supplied as an orange, film-coated tablet.

- Evening dose: 1 tablet containing 150 mg IVA, supplied as a blue, film-coated tablet.

The dose is to be taken approximately 12 hours apart. Both Kaftrio and Kalydeco tablets should be taken with fat containing food.

Based on the study results in F/MF (study 102) and F/F (study 103) patients, and the long-term results of these patient populations in study 105, Kaftrio was approved in August 2020 with the following indication:

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

At that time, it was concluded that the presented information was too limited to claim the F/any indication as the evidence for the *F508del*-only hypothesis was considered not definitively conclusive. Especially the added benefit over approved therapies in the F/RF and F/G population was questioned. Therefore, it was concluded that the data of study 104 in F/G and F/RF patients will meaningfully contribute to the understanding of the efficacy in the F/RF and F/G patient populations. The data of study 104 were required to show a clear benefit in F/RF and F/G patients before the approval of the broad F508del/any indication requested by the MAH can be considered.

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

No advice was requested/provided in relation to the study 104 in F/RF and F/G patient specifically.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No new ERA data have been submitted.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. The data submitted in this application are not expected to lead to a significant increase in environmental exposure further to the use of elexacaftor, ivacaftor and tezacaftor.

2.2.3. Conclusion on the non-clinical aspects

Considering the above information, elexacaftor, ivacaftor and tezacaftor is not expected to pose a risk to the environment.

However, the Ph II studies requested during the initial authorisation will need to be submitted as follow-up measure, as agreed, to complete the ERA assessment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

No GCP inspections were conducted for Study 104.

- Tabular overview of clinical studies

The list of studies performed with Kaftrio since initial approval is provided below. In this application study 104 and study 110 (cut off 30 June 2020) were provided.

Table 1: Tabular overview of clinical studies

STUDY NUMBER	STUDY DESCRIPTION
STUDIES IN HEALTHY SUBJECTS (OR PATIENT WITHOUT CF IN STUDY 007)	
STUDY 001 (PARTS A, B AND C)	Single-dose and multiple-dose escalation study and BA study of ELX monotherapy, or ELX/TEZ/IVA
STUDY 001 (PARTS A QT)	Cardiodynamic analysis of the effect of ELX on QTc interval
STUDY 002	DDI study of the effect of ELX/TEZ/IVA on the PK of oral contraceptives
STUDY 003	Mass balance study to investigate the absorption, distribution, metabolism and excretion of ELX
STUDY 005	BA study of ELX/TEZ/D-IVA and ELX/TEZ/IVA FDC tablets and food effects of ELX/TEZ/D-IVA FDC tablet
STUDY 006	DDI study of the effect of itraconazole on the PK of ELX/TEZ/D-IVA
STUDY 007	Evaluate the safety, tolerability, and PK of ELX/TEZ/IVA in subjects with moderate hepatic impairment
STUDY 009	Thorough QT/QTc study of ELX
STUDIES IN SUBJECTS WITH CF	
STUDY 001 (PARTS D, E AND F)	Safety and efficacy of ELX/TEZ/IVA and ELX/TEZ/D-IVA (F/MF and F/F subjects)
STUDY 102	Efficacy and safety of ELX/TEZ/IVA (F/MF subjects)
STUDY 103	Efficacy and safety of ELX/TEZ/IVA (F/F subjects)
STUDY 104	Efficacy and safety of ELX/TEZ/IVA (F/RF and F/G subjects)
STUDY 105	Open-label long term efficacy and safety of ELX/TEZ/IVA (F/MF and F/F subjects)
STUDY 110	Open-label long term efficacy and safety of ELX/TEZ/IVA (F/RF and F/G subjects)

2.3.1. Pharmacokinetics

The MAH has measured the pre-dose concentration values of each analyte (ELX, TEZ, IVA, and relevant metabolites) in study 104 and presented it as summary statistics by treatment group and for individual concentrations (Table 2).

Based on an assessment of pre-dose concentrations, ELX and M23-ELX reached steady-state by Day 15. Subjects received IVA or TEZ/IVA during the Run-in Period before Day 1; therefore, steady-state exposures of IVA, M1-IVA, TEZ, and M1-TEZ were achieved before entering the Treatment Period and were maintained through Week 8.

Table 2 Summary of Predose Concentrations (Ctrough) by Visit for Plasma Analytes.

	Visit and Statistic											
	Day 1			Day 15			Week 4			Week 8		
Treatment Group Analyte	N	Mean (SD) (µg/mL)	CV (%)	N	Mean (SD) (µg/mL)	CV (%)	N	Mean (SD) (µg/mL)	CV (%)	N	Mean (SD) (µg/mL)	CV (%)
ELX/TEZ/IVA												
ELX	129	BQL	NR	111	6.94 (4.22)	60.8	108	7.01 (4.07)	58.0	109	6.47 (3.67)	56.7
M23-ELX	129	BQL	NR	111	4.29 (2.96)	69.0	108	4.41 (3.12)	70.7	109	3.91 (2.77)	71.0
IVA	129	0.936 (0.648)	69.3	111	1.18 (0.821)	69.5	108	1.21 (0.861)	71.3	109	1.03 (0.813)	78.9
M1-IVA	129	1.91 (1.06)	55.6	111	2.49 (1.47)	59.0	108	2.70 (1.56)	57.9	109	2.41 (1.49)	61.9
TEZ	129	1.78 (1.87)	105	111	3.00 (1.62)	54.0	108	3.07 (1.69)	55.0	109	2.71 (1.54)	56.7
M1-TEZ	129	3.92 (3.53)	90.1	111	5.83 (2.12)	36.3	108	6.29 (2.22)	35.3	109	6.02 (2.17)	36.1
IVA												
IVA	43	0.698 (0.442)	63.4	43	0.780 (0.478)	61.3	40	0.705 (0.423)	60.0	38	0.742 (0.493)	66.5
M1-IVA	43	1.43 (0.819)	57.1	43	1.55 (0.765)	49.2	40	1.51 (0.739)	48.9	38	1.46 (1.02)	69.7
TEZ/IVA												
IVA	81	0.997 (0.662)	66.4	70	0.901 (0.591)	65.6	66	0.919 (0.549)	59.7	67	0.977 (0.628)	64.2
M1-IVA	81	2.11 (1.35)	64.0	70	1.82 (0.973)	53.4	66	1.90 (0.920)	48.4	67	2.12 (1.26)	59.5
TEZ	81	2.71 (1.48)	54.6	70	2.47 (1.29)	52.3	66	2.69 (1.26)	46.8	67	2.65 (1.15)	43.5
M1-TEZ	81	6.16 (1.92)	31.2	70	5.81 (2.01)	34.6	66	6.17 (1.93)	31.2	67	5.95 (1.87)	31.4

Source: Table 14.4.2.1
CV: coefficient of variation; BQL: below quantifiable levels; ELX: elexacaftor; IVA: ivacaftor; NR: not reported; TEZ: tezacaftor

2.3.2. Discussion on clinical pharmacology

The MAH has measured the pre-dose concentration values of each analyte (ELX, TEZ, IVA, and relevant metabolites) in study 104 and presented it as summary statistics by treatment group and for individual concentrations.

Based on an assessment of pre-dose concentrations, ELX and M23-ELX appeared to reach steady-state by Day 15. Subjects received IVA or TEZ/IVA during the Run-in Period before Day 1; therefore, steady-state exposures of IVA, M1-IVA, TEZ, and M1-TEZ were achieved before entering the Treatment Period and were maintained through Week 8. Exposures of all analytes were consistent with those observed in previous ELX/TEZ/IVA studies 102 and 103 submitted for the initial marketing authorisation.

2.3.3. Conclusions on clinical pharmacology

Exposures of all analytes in study 104 were consistent with those observed in previous ELX/TEZ/IVA studies 102 and 103. Overall, the pharmacokinetics and pharmacodynamics of Kaftrio have been adequately investigated and are correctly reflected in the SmPC.

2.4. Clinical efficacy

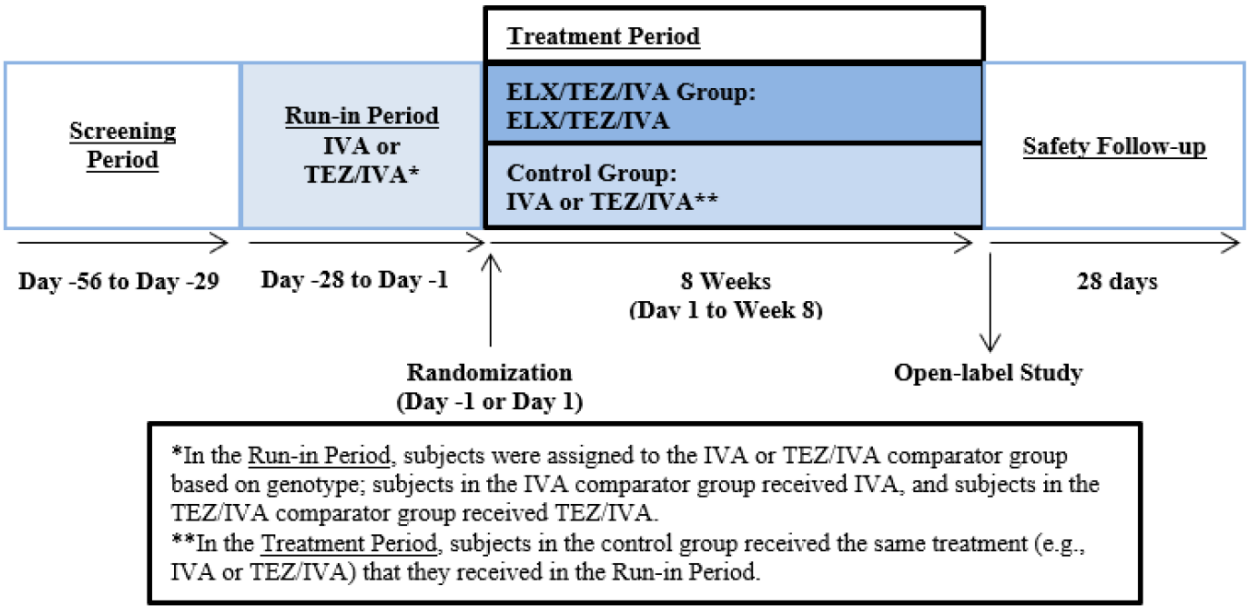
2.4.1. Main study: VX18-445-104 (study 104)

Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of Elexacaftor Combination Therapy in Subjects With Cystic Fibrosis who are heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF Genotypes).

Methods

This was a Phase 3, randomised, double-blind, active-controlled, parallel-group, multicentre study. In the open-label Run-in Period, subjects were assigned to the IVA or TEZ/IVA comparator group based on genotype and received the approved doses of the products (See Table 3). After completing the run-in, subjects were randomised (1:1) to the ELX/TEZ/IVA or control group (IVA or TEZ/IVA).

Figure 1: Schematic study design study 104



ELX: elexacaftor; IVA: ivacaftor; TC: triple combination; TEZ: tezacaftor
Note: The Safety Follow-up Visit was not required for subjects who completed the Week 8 Visit and enrolled in an open-label study within 28 days after the last dose of study drug.

Table 3: IVA and TEZ/IVA comparator group mutations

IVA Comparator Group Mutations[a]		
R117H	*G551D*	*G1244E*
G178R	*G551S*	*S1251N*
S549N	*G1069R*	*S1255P*
S549R	*R1070Q*	*G1349D*
TEZ/IVA Comparator Group Mutations[a]		
711+3A>G	*R117C*	*S977F*
2789+5G>A	*E193K*	*F1052V*
3272-26A>G	*L206W*	*K1060T*
3849+10kbC>T	*R347H*	*A1067T*
E56K	*R352Q*	*R1070W*
P67L	*A455E*	*F1074L*
R74W	*D579G*	*D1152H*
D110E	*E831X*	*D1270N*
D110H	*S945L*	

IVA: ivacaftor; TEZ: tezacaftor

[a] Refer to Appendix 16.1.1/Protocol Version 2.0/Appendix A, Appendix 16.1.1/Protocol Version 2.1CAN/ Appendix A, Appendix 16.1.1/Protocol Version 2.2EUR/Appendix A, and Appendix 16.1.1/Protocol Version 2.3AUS/Appendix A for qualifying mutations in each region.

Study participants

The *key inclusion criteria* of study 104 were that subjects are aged 12 years and older, have FEV1 value ≥40% and ≤90% of predicted mean for age, sex, race and height, a confirmed diagnosis of CF by the investigator and stable CF disease as judged by the investigator.

In addition, subjects were heterozygous for F508del and either a gating or residual function mutation (F/G and F/RF genotypes) and was in a region where their genotype and age group were approved indications for treatment with IVA and/or TEZ/IVA

The main *exclusion criteria* were:

1. Any of the following abnormal laboratory values at screening:
    a. Hemoglobin <10 g/dL
    b. Total bilirubin ≥2 × upper limit of normal (ULN)
    c. Aspartate transaminase (AST), alanine transaminase (ALT), or gamma-glutamyl transferase (GGT) ≥3 × ULN,
    d. Abnormal renal function defined as estimated glomerular filtration rate ≤50 mL/min/1.73 m2 (calculated by the Modification of Diet in Renal Disease Study Equation) for subjects ≥18 years of age and ≤45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive).
2. An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug in the Run-in Period (Day -28)
3. Lung infection with microbial pathogen associated with a more rapid decline in pulmonary status (including, but not limited to, Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus). For subjects who had a history of a positive culture, the

investigator applied the following criteria to establish whether the subject was free of infection with such organisms:

a. The subject did not have a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.

b. The subject had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.

Treatments

The treatment regimens used in study 104 are depicted in Table 4.

Table 4: Treatment groups and dosages

Comparator Group	Treatment Group	ELX Dosage	TEZ Dosage	IVA Dosage
IVA	ELX/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	0 mg	150 mg q12h
TEZ/IVA	ELX/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	100 mg qd	150 mg q12h

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

Study drug was administered within 30 minutes of consumption of fat-containing food, such as a standard "CF" meal or snack by the subject. No dose modifications for toxicity were allowed. Treatment was however permitted to be interrupted for toxicity. If any unacceptable toxicity arose, individual subjects discontinued dosing. Patients were allowed to receive usual standard of care treatment as prescribed by their doctor for their disease, with the caveat that they were to have been stable on their regime for at least 28 days prior to Day -28. Subjects were permitted to receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days. Information about bronchodilator use during the study was collected and documented.

Test product, batch/lot numbers:

ELX 100-mg/TEZ 50-mg/IVA 75-mg fixed-dose combination (FDC) tablet, TEZ 100-mg/IVA 150-mg FDC tablet, and IVA 150-mg tablet for oral administration.

Reference (placebo) therapy, batch/lot numbers:

ELX 0-mg/TEZ 0-mg/IVA 0-mg FDC tablet, TEZ 0-mg/IVA 0-mg FDC tablet, and IVA 0-mg tablet for oral administration.

Because this study has recruited both F/G and F/RF genotypes and randomised them as one, there are 2 different active controls: IVA for the F/G patients and TEZ/IVA for the F/RF patients, which is appropriate. Allowing SOC (provided that they were stable on this SOC for 28 days) on top of study treatment is appropriate.

Objectives

Primary Objective:

To evaluate the efficacy of ELX/TEZ/IVA in CF subjects who are heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes).

Secondary Objectives:

- To evaluate the safety of ELX/TEZ/IVA
- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA

Outcomes/endpoints

Primary Endpoint:

Absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group

Key Secondary Endpoints:

- Absolute change in sweat chloride (SwCl) from baseline through Week 8 for the ELX/TEZ/IVA group
- Absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group
- Absolute change in SwCl from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group

Other Secondary Endpoints:

- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score from baseline through Week 8 for the ELX/TEZ/IVA group
- Absolute change in CFQ-R RD score from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Exploratory Endpoints:

1. Absolute change in CFQ-R non-RD scores from baseline through Week 8
2. Absolute change in body mass index (BMI) from baseline at Week 8
3. Inflammatory mediators
4. Blood biomarkers

In general, the primary analyses were conducted with clinic data only. Due to the coronavirus disease (COVID-19) pandemic, home-assessed spirometry (i.e., spirometry assessed independently by the subjects at home) was permitted to be performed for the pulmonary endpoints. An additional analysis was performed that included pooled clinic and home-assessed spirometry.

Due to the pandemic, CFQ-R was also permitted to be performed at home. The main analysis included pooled CFQ-R data assessed at the clinic and at home. An additional analysis was performed that included only the CFQ-R data assessed at the clinic. Another prespecified analysis was performed that

included only the CFQ-R data from subjects who completed the Week 8 Visit before the outbreak of COVID-19 (defined as 02 March 2020).

Sample size

The primary efficacy endpoint was the absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group. The primary null hypothesis was to be tested is that the mean absolute change in ppFEV1 from baseline through Week 8 is 0 for the ELX/TEZ/IVA treatment group. The null hypothesis was to be tested at a 2-sided significance level of 0.05.

For the primary hypothesis, assuming a within-group standard deviation (SD) of 7.0 percentage points and a 10% dropout rate at Week 8, a sample size of 125 subjects in the ELX/TEZ/IVA arm will have >99% power to detect the within-group difference of 3.0 percentage points (1 sample t-test at a 2-sided significance level of 0.05).

Randomisation

Following the Run-in Period, subjects were randomised 1:1 to either the ELX/TEZ/IVA group or the control group. Randomisation was stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), ppFEV1 as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L).

Blinding (masking)

Study 104 was a double-blind study. All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes, with the exception of the following study personnel:

1. Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
2. Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
3. Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
4. Vendor preparing the final (production) randomisation list
5. Vertex IWRS Manager
6. Vertex Clinical Supply Chain
7. IDMC
8. Vendor preparing the unblinded analysis of data for safety review by the IDMC
9. Bioanalytical contract research organisation (CRO) analysing PK samples and the Vertex bioanalytical personnel who is not a member of the study team but reviews raw data from the bioanalytical CRO. The Vertex bioanalytical study team member will continue to be blinded.

If unblinding was needed to respond to an emergency, the unblinded treatment code was only revealed to those personnel who needed to know the code to respond to the safety concern.

Spirometry and SwCl results were also not revealed during the course of the study to the patients, investigators, or to the Vertex team- with the exception of SwCl values screening and Day -14 only.

Statistical methods

Statistical Analysis Plan

Version 2.0 of the SAP is dated 22 June 2020. The SAP was amended to account for implemented measures to minimise risk to COVID-19 exposure. The MAH states that this was prior to database lock. Key changes to analyses in Version 1.0 of the SAP (06 March 2020) are summarised below:

Table 5: Summary of Study VX18-445-104 SAP Changes

Version Number	Date	Key Changes
1.0	06 March 2020	Original version
2.0	22 June 2020	• Clarified that the primary analysis for ppFEV$_1$ was based on clinic spirometry only. • Clarified that the main analysis for CFQ-R RD score included both clinic and home-assessed CFQ-R data. • Added a listing containing subjects' visits impacted by COVID-19 to meet regulatory agency-issued guidance on clinical studies conducted during the pandemic.

CFQ-R: Cystic Fibrosis Questionnaire–Revised; COVID-19: coronavirus disease; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain

The study completed on 12 June 2020 (date last subject completed last visit). The database lock date was 30 June 2020.

Changes to the Planned analyses

There were no changes to the planned analyses described in SAP version 2.0.

Analysis Populations

The following analysis sets were defined: All Subjects Set, Full Analysis Set, Safety Set for the Run-in Period and Safety Set for the Treatment Period.

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

The **Full Analysis Set** (FAS) was to include all randomised subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug in the Treatment Period. The FAS was to be used to summarise subject demographics and baseline characteristics, and for all efficacy analyses in which subjects were to be analysed according to their randomised treatment group unless otherwise specified.

The **Safety Set for the Run-in Period** was to include all subjects who receive at least 1 dose of TEZ/IVA or IVA in the Run-in Period. This safety set was to be included in individual subject data listings unless otherwise specified.

The **Safety Set for the Treatment Period** was to include all subjects who receive at least 1 dose of study drug in the Treatment Period. This safety set was to be used for all safety analyses in which subjects was to be analysed according to the treatment they receive, unless otherwise specified.

Analysis of primary endpoint – absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group

The primary efficacy variable was the absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group. Percent predicted FEV1 is the ratio of FEV1 (L) to the predicted FEV1 (L), expressed as a percentage. The predicted FEV1 was to be calculated using the Global Lung Function Initiative1 (GLI).

The primary analysis was to be performed using a mixed-effects model for repeated measures (MMRM) with the absolute change from baseline at Day 15, Week 4 and Week 8 as the dependent variable. The model was to include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV1, continuous baseline SwCl, and comparator group (IVA comparator vs TEZ/IVA comparator) as covariates. The model was to be estimated using restricted maximum likelihood.

Denominator degrees of freedom for the *F*-test for fixed effects were to be estimated using the Kenward-Roger approximation. An unstructured covariance structure was to be used to model the within-subject errors. If the model estimation did not converge, a compound symmetry covariance structure was to be used instead. Conditional on the observed data and covariates, missing data was to be assumed to be missing at random; consequently, no imputation of missing data was to be performed.

The primary result obtained from the model was to be the estimated within-group treatment difference through week 8 (average of week 4 and week 8) for the ELX/TEZ/IVA group. The adjusted means with 2-sided 95% confidence intervals and 2-sided *P* values were to be provided. Furthermore, the within-group treatment difference at each post-baseline visit obtained from the model was also to be provided. The adjusted mean (with SE) obtained from the MMRM analysis at each post-baseline visit up to Week 8 was to be plotted by treatment group.

The primary analysis was to be conducted with the clinic spirometry data only. An additional analysis may also be performed to include pooled spirometry data obtained in clinic and by Air Next Spirometer, if the Air Next Spirometry data are assessed to be reasonably consistent with clinic spirometry data.

Handling of missing data in primary endpoint

Subjects who prematurely discontinued study drug treatment were to continue to complete all scheduled study visits for spirometry and other efficacy assessments.

To assess the impact of missing data and the assumption that data are missing at random, a multiple imputation algorithm was to be used if at least 10% of the subjects had missing changes in ppFEV1 at Week 8 in any treatment group. Missing absolute change from baseline in ppFEV1 assessments were to be imputed starting from the first visit with missing values, for which all subsequent visits through Week 8 are also missing. For intermediate missing data, i.e., missing values that fall between two non-missing ones were not to be imputed as it was assumed that MAR assumption was reasonable for these data. An MMRM analogous to that for the primary analysis of the primary endpoint was to be applied to each imputed dataset (K=20) and the relevant Rubin's rules MI estimators were to be reported.

The imputation distribution for the missing absolute change from baseline in ppFEV1 at visit t was to be a normal distribution. All randomised subjects were to be classified into one of three categories based on the following rules:

- Non-missing category: Subjects who had a ppFEV1 assessment at Week 8 (i.e., subjects who had a non-missing absolute change from baseline in ppFEV1 at Week 8).
- Missing category 1: Subjects with missing absolute change from baseline in ppFEV1 at Week 8, who discontinued treatment because of adverse events, noncompliance with study drug, death, or physician decision, or because the subject refused further dosing or required prohibited medication.
- Missing category 2: Subjects who discontinued treatment for any reason not listed in Category 1 and have missing absolute change from baseline in ppFEV1 at Week 8, or subjects who have completed 8 weeks treatment duration but are missing the absolute change from baseline in ppFEV1 at visit Week 8

The following imputation algorithm was to be implemented within each treatment group as follows:

- Missing category 1: randomly draw a sample from the normal distribution (μ_{25}, σ^2), where μ_{25} is the 25th percentile of the non-missing absolute changes from baseline in ppFEV1 at visit *t* and σ^2 is the sample variance estimated using the non-missing absolute changes at visit *t*.
- Missing category 2: randomly draw a sample from the normal distribution (μ,^{2}), where μ is the mean of the non-missing absolute changes from baseline in ppFEV1 at visit *t* and σ^2 is the sample variance estimated using the non-missing absolute changes at visit *t*.

Analysis of ranked secondary variables

Sweat chloride (SwCl): the SwCl value for a given visit was to be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point was missing, the other was to be used as the mean. A volume of ≥15 µL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 µL were to be considered missing. Any sweat chloride values reported as >160 mmol/L were to be considered missing. Any sweat chloride values reported as <10 mmol/L was to be imputed as 10 mmol/L.

Analysis of **absolute change in SwCl from baseline through week 8 for the ELX/TEZ/IVA group** was to be based on the same MMRM similar as the primary analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits were to be included in the model. Absolute change in SwCl from baseline through Week 8 was defined as the average of Day 15, Week 4, and Week 8.

Analysis of **absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group** was to be based on the same MMRM model as the primary analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits were to be included in the model. However, the Day 15 Visit was not to be included in the estimation of the average treatment effect through Week 8.

Analysis of **absolute change in SwCl from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group** was to be based on the same MMRM model as the primary analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits were to be included in the model. Absolute change in SwCl from baseline through Week 8 was defined as the average of Day 15, Week 4, and Week 8.

The LS mean (SE) of the within-treatment group change from baseline at each post-baseline visit up to Week 8 along with the 95% CI was to be estimated from the corresponding MMRM. The LS mean (SE) of the treatment difference between ELX/TEZ/IVA and control at each post-baseline visit was to be

provided along with the corresponding 95% CI and *P* value. The LS mean (SE) at each visit was also be plotted by treatment group. In addition, the post-baseline raw values and the absolute change from baseline at each post-baseline visit up to Week 8 were to be summarised descriptively (n, mean, SD, median, minimum, and maximum).

To assess the impact of including extreme small sweat chloride values, a sensitivity analysis was to be conducted in which case any sweat chloride values reported as <10 mmol/L were to be considered as missing. This sensitivity analysis only applies to the absolute change from baseline in SwCl.

Subgroup analyses

Subgroup analyses of the primary efficacy endpoint were to be performed using a model similar to that of the primary analysis for each of the following subgroups. The primary result obtained from the model will be estimated within-treatment difference through Week 8 (average of Week 4 and Week 8) for the ELX/TEZ/IVA group:

- Age at Screening (<18, ≥18 years)
- ppFEV1 at baseline (< 70, ≥ 70)
- Comparator group (TEZ/IVA comparator, IVA comparator)
- Sex (male, female)
- Geographic region (North America, Europe)

The MMRM used for the primary analysis was to be used for the subgroup analysis, where the same model was to be applied to each category of the subgroup. Note that for the subgroup analysis based on comparator group, the covariate of comparator group (TEZ/IVA comparator, IVA comparator) from the MMRM were to be removed. The adjusted means with 2-sided 95% confidence intervals were to be provided. Furthermore, estimated within-treatment differences through Week 8 (average of Week 4 and Week 8) for the ELX/TEZ/IVA group in different categories within a subgroup were also to be presented in a forest plot.

Multicentre studies

Subgroup analyses of the primary efficacy endpoint for geographic region (North America, Europe) were planned.

Type I error control

A hierarchical testing procedure was to be used to control the type I error rate at an alpha of 0.05 for the primary and key secondary endpoints. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The key secondary endpoints were to be formally tested at an alpha of 0.05 only if the primary endpoint is statistically significant. The testing order of the key secondary endpoints was as follows:

- Absolute change in SwCl from baseline through Week 8 for the ELX/TEZ/IVA group
- Absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group
- Absolute change in SwCl from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group.

Results

Participant flow

During the Run-in Period, 6 subjects discontinued the study for reasons related to the COVID-19 pandemic, including 1 subject who had an AE of coronavirus infection.

Of the 258 subjects who received at least 1 dose of study drug in the Treatment Period, 5 (1.9%) subjects discontinued treatment and the study; although no subject was diagnosed with COVID-19, 1 subject discontinued the study for reasons related to the COVID-19 pandemic (physician decision due to restrictions for on-site visits).

The subject disposition of the Treatment Period is depicted in Table 6.

Table 6: Subject disposition, treatment period (All Subjects Set)

Disposition/Reason, n (%)	Control	ELX/TEZ/IVA	Total
Full Analysis Set	126	132	258
Safety Set for the Treatment Period	126	132	258
Randomized	126	133	259
Randomized but not dosed in the Treatment Period	0	1	1
Randomized or dosed in the Treatment Period	126	133	259
Completed treatment	122 (96.8)	131 (99.2)	253 (98.1)
Prematurely discontinued randomized treatment	4 (3.2)	1 (0.8)	5 (1.9)
Reason for discontinuation of randomized treatment			
AE	2 (1.6)	1 (0.8)	3 (1.2)
Physician decision	1 (0.8)	0	1 (0.4)
Pregnancy (self or partner)	1 (0.8)	0	1 (0.4)
Completed study[a]	122 (96.8)	131 (99.2)	253 (98.1)
Prematurely discontinued study in TE Period	4 (3.2)	1 (0.8)	5 (1.9)
Reason for discontinuation from study in TE Period			
AE	2 (1.6)	1 (0.8)	3 (1.2)
Withdrawal of consent (not due to AE)	0	0	0
Lost to follow-up	0	0	0
Commercial drug is available for subject	0	0	0
Death	0	0	0
Other non-compliance	0	0	0
Physician decision	1 (0.8)	0	1 (0.4)
Sponsor decision	0	0	0
Study termination by sponsor	0	0	0
Other	1 (0.8)	0	1 (0.4)
Rollover to open-label study			
Yes	121 (96.0)	130 (98.5)	251 (97.3)
No	5 (4.0)	2 (1.5)	7 (2.7)

Source: Table 14.1.1.2

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; TE: Treatment-emergent; TEZ: tezacaftor

Notes: Full Analysis Set was defined as all randomized subjects who carry the intended *CFTR* allele mutation(s) and have received at least 1 dose of study drug in the Treatment Period. Safety Set for the Treatment Period was defined as all subjects who received at least 1 dose of the study drug in the Treatment Period. Percentages were based on the number of subjects in the Safety Set for the Treatment Period.

[a] Subjects who completed the Week 8 Visit and either entered an open-label study within 28 days or completed the Safety Follow-up Visit.

Compliance was evaluated on an ongoing basis by the study team through review of missed doses, which were captured as protocol deviations.
No treatment compliance issues were identified.
A listing of subject visits impacted by the COVID-19 pandemic was provided; none of the events (e.g., videoconference or telephone contact visit) were considered to be IPDs. (see also conduct of the study).

Recruitment

The study was conducted at 96 sites in the US, Canada, EU and Australia.

The study period was from 28 August 2019 (date first eligible subject signed the informed consent form) to 12 June 2020 (date last subject completed the last visit).

Patients were followed up for 28 days after study cessation, or patients moved to the open label study within 28 days of stopping study drug.

Conduct of the study

The global study protocol was amended once. The only amendment was included in all protocols in December 2019. Absolute change in BMI from baseline at Week 8 was added as an exploratory endpoint to meet an FDA post-marketing commitment.

Changes in conduct Due to COVID-19

The MAH implemented safety measures to provide subjects with the opportunity to continue participation in Study 104 while ensuring their safety by minimising the risk to COVID-19 exposure through travel. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimising impact to study integrity. A summary of these measures pertinent to Study 104 is summarised in Table 7.

Implemented measures were enabled based on the country and local regulations and site-level considerations (e.g., site closure due to COVID-19). Subjects' study visits impacted by COVID-19 include a small number of subjects who had blood and/or urine samples analysed at a local laboratory for safety monitoring. The MAH developed a cross-study local laboratory database for ease of data collection.

At the time of EDC database lock for this study, the cross-study local laboratory database was still being validated; therefore, local laboratory data for this study were not entered and not included in this CSR. However, in addition to their usual review of central laboratory data, investigators were responsible for reviewing local laboratory data to identify potential AEs.

Table 7: Summary of implemented measures to minimise risk for COVID-19 exposure

Addendum Version	Date	Key Changes and Rationale	Date Implemented
1.0	24 April 2020	Remote telephone consent was permitted for protocol amendments and/or COVID-19 related addenda to minimize COVID-19 exposure. ICF forms were then signed and dated before sending to the site via post mail.	17 March 2020
		Study drug was permitted to be dispensed to subjects outside of the context of an in-clinic visit (e.g., shipped directly from the site to the subject), as applicable, and if permitted by local regulations.	17 March 2020
		Study visits were permitted to be conducted as in-home visits by qualified personnel. In addition, all subjects were permitted to be contacted by site personnel by telephone/video call.	In-home visits: 05 May 2020 Telephone/video contact: 16 March 2020
		Safety assessments were permitted to be performed by qualified personnel conducting in-home visits. Blood and/or urine samples for safety assessments were permitted to be collected and analyzed at local laboratories for subjects who did not have in-home visits, but did not complete the assessment at the site. In addition, safety assessments were permitted to be evaluated by telephone.	In-home safety assessments: 05 May 2020 Telephone safety assessments: 16 March 2020 Use of local laboratories: 17 March 2020
		Efficacy assessments (i.e., spirometry, CFQ-R) were permitted to be performed by subjects at home.[a]	01 April 2020
		Remote monitoring visits, including remote source data verification, were permitted as allowed per local regulations.[b] The study team reviewed the risk assessment and prioritized data based on primary endpoints, key secondary endpoints, and safety. These details are present in the monitoring plan.	24 April 2020
2.0[c]	15 May 2020	Provided examples of qualified personnel (e.g., personnel from site or qualified health care agency) who could conduct safety assessments, as indicated per protocol, during in-home visits.	15 May 2020

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

[a] Addendum 1 also allowed for SwCl to be collected at home. However, this measure was not enabled for Study 104; all SwCl assessments occurred in clinic.

[b] Belgium and France did not permit remote source data verification per their regulatory guidances; all other COVID-19 measures were implemented globally.

[c] Addendum 2 also allowed for weight and height to be collected by subjects or their caregivers; however, these measures were not implemented for this study.

Baseline data

Demographics and baseline characteristics

The demographic and baseline characteristics are provided in Table 8 and in Table 9, respectively. In general, the demographic and baseline characteristics are balanced between the two treatment groups.

Table 8: Subject Demographics (FAS)

Demographic	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
Sex, n (%)			
Male	65 (51.6)	65 (49.2)	130 (50.4)
Female	61 (48.4)	67 (50.8)	128 (49.6)
Childbearing potential, n (%)			
Yes	48 (78.7)	50 (74.6)	98 (76.6)
No	13 (21.3)	17 (25.4)	30 (23.4)
Age at baseline (years)			
n	126	132	258
Mean (SD)	37.6 (14.3)	37.7 (14.7)	37.7 (14.5)
Median	37.9	37.2	37.5
Min, max	13.4, 72.7	12.3, 69.8	12.3, 72.7
Ethnicity, n (%)			
Hispanic or Latino	4 (3.2)	5 (3.8)	9 (3.5)
Not Hispanic or Latino	114 (90.5)	117 (88.6)	231 (89.5)
Not collected per local regulations	8 (6.3)	10 (7.6)	18 (7.0)
Race, n (%)			
White	111 (88.1)	122 (92.4)	233 (90.3)
Black or African American	2 (1.6)	0	2 (0.8)
Asian	0	0	0
American Indian or Alaska Native	1 (0.8)	0	1 (0.4)
Native Hawaiian or other Pacific Islander	0	0	0
Other	4 (3.2)	1 (0.8)	5 (1.9)
Not collected per local regulations	9 (7.1)	9 (6.8)	18 (7.0)
Geographic Region, n (%)			
North America	48 (38.1)	49 (37.1)	97 (37.6)
Europe	64 (50.8)	70 (53.0)	134 (51.9)
Australia	14 (11.1)	13 (9.8)	27 (10.5)

Sources: Table 14.1.3 and Ad Hoc Table 14.1.3.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. Percentages of childbearing women were based on the number of women in the FAS. If a subject was reported to have multiple races, then the subject was counted for each race reported.

Table 9: Baseline characteristics (FAS)

Characteristic	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
Weight (kg)			
Mean (SD)	69.6 (17.4)	69.5 (16.6)	69.5 (17.0)
Median	67.0	67.4	67.0
Min, max	41.0, 133.0	37.0, 125.2	37.0, 133.0
Height (cm)			
Mean (SD)	169.4 (9.2)	169.3 (9.7)	169.4 (9.5)
Median	169.0	169.0	169.0
Min, max	146.0, 191.0	150.0, 189.0	146.0, 191.0
BMI (kg/m^2)			
Mean (SD)	24.05 (4.71)	24.07 (4.72)	24.06 (4.71)
Median	23.07	23.15	23.12
Min, max	16.51, 41.62	15.81, 44.36	15.81, 44.36
Age group at the Screening Visit, n (%)			
≥12 to <18	9 (7.1)	15 (11.4)	24 (9.3)
≥18	117 (92.9)	117 (88.6)	234 (90.7)
Comparator group, n (%)			
TEZ/IVA	81 (64.3)	82 (62.1)	163 (63.2)
IVA	45 (35.7)	50 (37.9)	95 (36.8)
$ppFEV_1$ category at the Day -14 Visit[a], n (%)			
<70	67 (53.2)	74 (56.1)	141 (54.7)
≥70	59 (46.8)	58 (43.9)	117 (45.3)
SwCl (mmol/L) at the Day -14 Visit[a], n (%)			
<30	24 (19.0)	24 (18.2)	48 (18.6)
≥30	102 (81.0)	108 (81.8)	210 (81.4)

Table 9: Baseline characteristics (FAS), continued

Characteristic	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
$ppFEV_1$ category at baseline, n (%)			
<40	2 (1.6)	2 (1.5)	4 (1.6)
≥40 to <70	63 (50.0)	70 (53.0)	133 (51.6)
≥70 to ≤90	52 (41.3)	53 (40.2)	105 (40.7)
>90	9 (7.1)	7 (5.3)	16 (6.2)
$ppFEV_1$ at baseline			
Mean (SD)	68.1 (16.4)	67.1 (15.7)	67.6 (16.0)
Median	68.6	68.3	68.3
Min, max	31.1, 104.1	29.7, 113.5	29.7, 113.5
SwCl (mmol/L) at baseline			
Mean (SD)	56.4 (25.5)	59.5 (27.0)	58.0 (26.3)
Median	54.0	56.8	55.8
Min, max	10.0, 109.5	10.0, 116.5	10.0, 116.5
CFQ-R RD score at baseline			
Mean (SD)	77.3 (15.8)	76.5 (16.6)	76.9 (16.2)
Median	77.8	77.8	77.8
Min, max	11.1, 100.0	0.0, 100.0	0.0, 100.0
Prior use of dornase alfa[b], n (%)			
Yes	66 (52.4)	69 (52.3)	135 (52.3)
No	60 (47.6)	63 (47.7)	123 (47.7)
Prior use of azithromycin[b], n (%)			
Yes	57 (45.2)	57 (43.2)	114 (44.2)
No	69 (54.8)	75 (56.8)	144 (55.8)
Prior use of inhaled antibiotic[b], n (%)			
Yes	56 (44.4)	49 (37.1)	105 (40.7)
No	70 (55.6)	83 (62.9)	153 (59.3)
Prior use of any bronchodilator[b], n (%)			
Yes	111 (88.1)	113 (85.6)	224 (86.8)
No	15 (11.9)	19 (14.4)	34 (13.2)
Prior use of any inhaled bronchodilator[b], n (%)			
Yes	108 (85.7)	111 (84.1)	219 (84.9)
No	18 (14.3)	21 (15.9)	39 (15.1)
Prior use of any inhaled hypertonic saline[b], n (%)			
Yes	54 (42.9)	57 (43.2)	111 (43.0)
No	72 (57.1)	75 (56.8)	147 (57.0)
Infection with *Pseudomonas aeruginosa* within 2 years prior to screening, n (%)			
Positive	74 (58.7)	79 (59.8)	153 (59.3)
Negative	52 (41.3)	53 (40.2)	105 (40.7)

Source: Table 14.1.4

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; 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; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. Baseline data were available for all subjects; therefore, n was identical to N and is not shown.

[a] If the Day -14 value was not valid or not available, the most recent available value was used.

[b] Includes medications started 56 days before the first dose of study drug in the Treatment Period.

Prior use of CFTR modulators

Table 10 provides the number of subjects with and without prior (within 56 days of study enrolment) IVA or TEZ/IVA usage by comparator group, consistent with the approach used to analyze the data

provided for Study 103 in the initial MAA. Prior usage of CFTR modulators was generally similar between the control group and the ELX/TEZ/IVA group for both F/G and F/RF subjects.

Table 10: Prior CFTR modulator (CFTRm) use in F/G and F/RF Subjects (Study 104 FAS)

	F/G (IVA Comparator Group)			F/RF (TEZ/IVA Comparator Group)		
Prior medication	Control N = 45 (%)	ELX/TEZ/IVA N = 50 (%)	Total N = 95 (%)	Control N = 81 (%)	ELX/TEZ/IVA N = 82 (%)	Total N = 163 (%)
Prior IVA	33 (73.3)	36 (72.0)	69 (72.6)	6 (7.4)	1 (1.2)	7 (4.3)
Prior TEZ/IVA	1 (2.2)	1 (2.0)	2 (2.1)	19 (23.5)	25 (30.5)	44 (27.0)
Any prior CFTRm	34 (75.6)	37 (74.0)	71 (74.7)	25 (30.9)	26 (31.7)	51 (31.3)

Source: Adhoc Table 14.1.4.3

CFTRm: cystic fibrosis transmembrane conductance regulator modulator; ELX: elexacaftor; FAS: Full Analysis Set; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a second allele that results in residual function; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

Notes: Prior to enrollment is defined as anytime that is within 56 days (excluding Run-in Period) before first dose date of study drug in the treatment period. Subjects who took both IVA and TEZ/IVA were counted in prior TEZ/IVA only.

Concomitant medications

Table 11 summarises concomitant medication received by at least 20% of subjects overall by PN. The most common concomitant medications (incidence of at least 20% of total subjects) were typically used for the management of CF. Table 12 summarizes concomitant medication by comparator group.

Table 11: Concomitant Medications Received by at Least 20% of subjects overall during the treatment period by PN (FAS)

PN, n (%)	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
Subjects with any concomitant medication during the Treatment Period	126 (100.0)	132 (100.0)	258 (100.0)
Salbutamol	72 (57.1)	80 (60.6)	152 (58.9)
Dornase alfa	66 (52.4)	70 (53.0)	136 (52.7)
Sodium chloride	66 (52.4)	68 (51.5)	134 (51.9)
Azithromycin	58 (46.0)	57 (43.2)	115 (44.6)
Pancreatin	51 (40.5)	49 (37.1)	100 (38.8)
Colecalciferol	38 (30.2)	44 (33.3)	82 (31.8)

Source: Table 14.1.6.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; PN: Preferred Name; TEZ: tezacaftor; WHODrug: World Health Organization Drug Dictionary

Notes: Medications were coded using WHODrug, version March 2020, format B3. PNs were sorted in descending order of frequency of the Total column. A subject with multiple medications with the same PN was counted only once for that PN. Concomitant medication during the Treatment Period was defined as any medication continued or newly received during the treatment-emergent period for the Treatment Period.

Table 12: Concomitant Medication by preferred name received by at least 20% of subjects in either comparator arm during the treatment period by comparator group (Study 104 FAS)

	F/G IVA Comparator Group			F/RF TEZ/IVA Comparator Group		
Preferred Name	Control N = 45 n (%)	ELX/TEZ/IVA N = 50 n (%)	Total N = 95 n (%)	Control N = 81 n (%)	ELX/TEZ/IVA N = 82 n (%)	Total N = 163 n (%)
Subjects with any concomitant medication during the Treatment Period	45 (100.0)	50 (100.0)	95 (100.0)	81 (100.0)	82 (100.0)	163 (100.0)
SALBUTAMOL	24 (53.3)	31 (62.0)	55 (57.9)	48 (59.3)	49 (59.8)	97 (59.5)
DORNASE ALFA	26 (57.8)	30 (60.0)	56 (58.9)	40 (49.4)	40 (48.8)	80 (49.1)
SODIUM CHLORIDE	29 (64.4)	25 (50.0)	54 (56.8)	37 (45.7)	43 (52.4)	80 (49.1)
AZITHROMYCIN	25 (55.6)	17 (34.0)	42 (44.2)	33 (40.7)	40 (48.8)	73 (44.8)
COLECALCIFEROL	11 (24.4)	13 (26.0)	24 (25.3)	27 (33.3)	31 (37.8)	58 (35.6)
PANCREATIN	28 (62.2)	31 (62.0)	59 (62.1)	23 (28.4)	18 (22.0)	41 (25.2)
COLISTIMETHATE SODIUM	5 (11.1)	4 (8.0)	9 (9.5)	19 (23.5)	16 (19.5)	35 (21.5)
PARACETAMOL	11 (24.4)	9 (18.0)	20 (21.1)	14 (17.3)	14 (17.1)	28 (17.2)

Source: Adhoc Table 14.1.6.2.1

ELX: elexacaftor; FAS: Full Analysis Set; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a second allele that results in residual function; IVA: ivacaftor; N: size of sample; n: size of subsample; TEZ: tezacaftor

Notes: Medications were coded using WHODD, version March 2020, format B3. Preferred Names are sorted in descending order of frequency of the last Total column. A subject with multiple medications with the same Preferred Name is counted only once for that Preferred Name. Concomitant medication during the Treatment Period were defined as medication continued or newly received during the treatment-emergent period for the Treatment Period.

Genotypes included

Subjects heterozygous for F508del and a gating or RF mutation listed in the protocol and in regions where their genotype and age group were approved indications for treatment with IVA and/or TEZ/IVA were eligible for the study. Only subjects with mutations that appeared in the regional mutation lists were included in the study. Table 13 presents the genotypes of subjects in the FAS by comparator group and treatment group. Among the subjects in the FAS, 14 distinct genotypes were represented in the TEZ/IVA comparator group, and 10 distinct genotypes were represented in the IVA comparator group.

Only one mutation (in one patient) was, in the end, recruited that is not approved in the EU, the RF mutation R347H (and that patient received control).

Of the 24 mutations (RF and G) recruited, 12 F/RFs and 7 F/Gs were represented (with at least one patient) in the ELX/TEZ/IVA treatment group; the remaining 5 were treated with appropriate control.

The most frequently represented F/RF genotypes recruited and treated had 3849 +10kbC> T (n=39), 2789+ 5G> A(n=34), A455E(n=22) and 3272-26A>G(n=20) as the non F allele. The most frequently represented F/G genotypes recruited and treated had G551D and R117H as the second allele, each with n=61 and n=16 patients recruited respectively.

Table 13: Subjects genotypes (FAS)

Comparator Group Genotype	Control N = 126 n (%)	ELX/TEZ/IVA N = 132 n (%)	Total N = 258 n (%)
TEZ/IVA comparator group	81 (64.3)	82 (62.1)	163 (63.2)
F508del/3849+10kbC>T	20 (15.9)	19 (14.4)	39 (15.1)
F508del/2789+5G>A	19 (15.1)	15 (11.4)	34 (13.2)
F508del/A455E	8 (6.3)	14 (10.6)	22 (8.5)
F508del/3272-26A>G	11 (8.7)	9 (6.8)	20 (7.8)
F508del/S945L	7 (5.6)	4 (3.0)	11 (4.3)
F508del/D1152H	3 (2.4)	7 (5.3)	10 (3.9)
F508del/P67L	5 (4.0)	5 (3.8)	10 (3.9)
F508del/L206W	1 (0.8)	5 (3.8)	6 (2.3)
F508del/R352Q	3 (2.4)	1 (0.8)	4 (1.6)
F508del/711+3A>G	1 (0.8)	1 (0.8)	2 (0.8)
F508del/R117C	1 (0.8)	1 (0.8)	2 (0.8)
F508del/D579G	0	1 (0.8)	1 (0.4)
F508del/R1070W	1 (0.8)	0	1 (0.4)
F508del/R347H	1 (0.8)	0	1 (0.4)
IVA comparator group	45 (35.7)	50 (37.9)	95 (36.8)
F508del/G551D	26 (20.6)	35 (26.5)	61 (23.6)
F508del/R117H	8 (6.3)	8 (6.1)	16 (6.2)
F508del/S1251N	4 (3.2)	1 (0.8)	5 (1.9)
F508del/G1244E	1 (0.8)	2 (1.5)	3 (1.2)
F508del/G178R	1 (0.8)	1 (0.8)	2 (0.8)
F508del/S1255P	0	2 (1.5)	2 (0.8)
F508del/S549N	2 (1.6)	0	2 (0.8)
F508del/S549R	1 (0.8)	1 (0.8)	2 (0.8)
F508del/G1349D	1 (0.8)	0	1 (0.4)
F508del/G551S	1 (0.8)	0	1 (0.4)

Source: Ad Hoc Table 14.1.10
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Treatment compliance

Similar to the already assessed pivotal studies for ELX/TEZ/IVA, overall treatment compliance rates were very high in Study 104. Of the 258 subjects in the FAS there was a mean compliance of 99.6% overall, 99.4% in the ELX/TEZ/IVA group and 99.7% in the control group. In both the treatment and control groups, 99.2% of subjects had a compliance category of ≥80%.

Numbers analysed

The FAS was used for efficacy analyses. There were 13 subjects in the All Subjects Set who were excluded from the FAS: 12 subjects discontinued the study during the Run-in Period and were never randomized, and 1 subject was randomized to the Treatment Period but not dosed. This left a FAS of

258 patients.

Of the 258 patients in the FAS, 253 (98.1%) completed dosing. 5 patients discontinued during the treatment period (see breakdown in table 6 in the participants' flow section), leaving 253 patients who completed the 8 week treatment period and the study. The percentage of subjects who discontinued treatment due to AE was low in both treatment groups (triple therapy group: 0.8%; control: 1.6%).

Outcomes and estimation

A summary of all efficacy data is included in Table 14.

Table 14: Study 104 primary, key secondary and other secondary efficacy analyses (FAS)

Statistic	Control N = 126	ELX/TEZ/IVA N = 132
Primary Endpoint		
Absolute change in **ppFEV$_1$** from baseline through Week 8 for the ELX/TEZ/IVA group (percentage points)		
n	--	115
LS mean (SE)	--	3.7 (0.5)
95% CI of LS mean	--	(2.8, 4.6)
P value within treatment	--	<0.0001
Key Secondary Endpoints		
Absolute change in **SwCl** from baseline through Week 8 for the ELX/TEZ/IVA group (mmol/L)		
n	--	120
LS mean (SE)	--	-22.3 (1.1)
95% CI of LS mean	--	(-24.5, -20.2)
P value within treatment	--	<0.0001
Absolute change in **ppFEV$_1$** from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group (percentage points)		
n	114	115
LS mean (SE)	0.2 (0.5)	3.7 (0.5)
95% CI of LS mean	(-0.7, 1.1)	(2.8, 4.6)
LS mean difference, 95% CI	--	3.5 (2.2, 4.7)
P value versus control	--	<0.0001
Absolute change in **SwCl** from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group (mmol/L)		
n	119	120
LS mean (SE)	0.7 (1.1)	-22.3 (1.1)
95% CI of LS mean	(-1.4, 2.8)	(-24.5, -20.2)
LS mean difference, 95% CI	--	-23.1 (-26.1, -20.1)
P value versus control	--	<0.0001
Other Secondary Endpoints		
Absolute change in **CFQ-R RD** score from baseline through Week 8 for the ELX/TEZ/IVA group (points)		
n	--	130
LS mean (SE)	--	10.3 (1.2)
95% CI of LS mean	--	(8.0, 12.7)
Nominal *P* value within treatment	--	<0.0001
Absolute change in **CFQ-R RD** score from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group (points)		
n	126	130
LS mean (SE)	1.6 (1.2)	10.3 (1.2)
95% CI of LS mean	(-0.8, 4.1)	(8.0, 12.7)
LS mean difference, 95% CI	--	8.7 (5.3, 12.1)
Nominal *P* value versus control	--	<0.0001

Sources: Study 104 CSR/Table 11-2, Table 11-3, Table 11-4, Table 11-5, Table 11-6, and Table 11-7
CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

Long function endpoints: FEV1

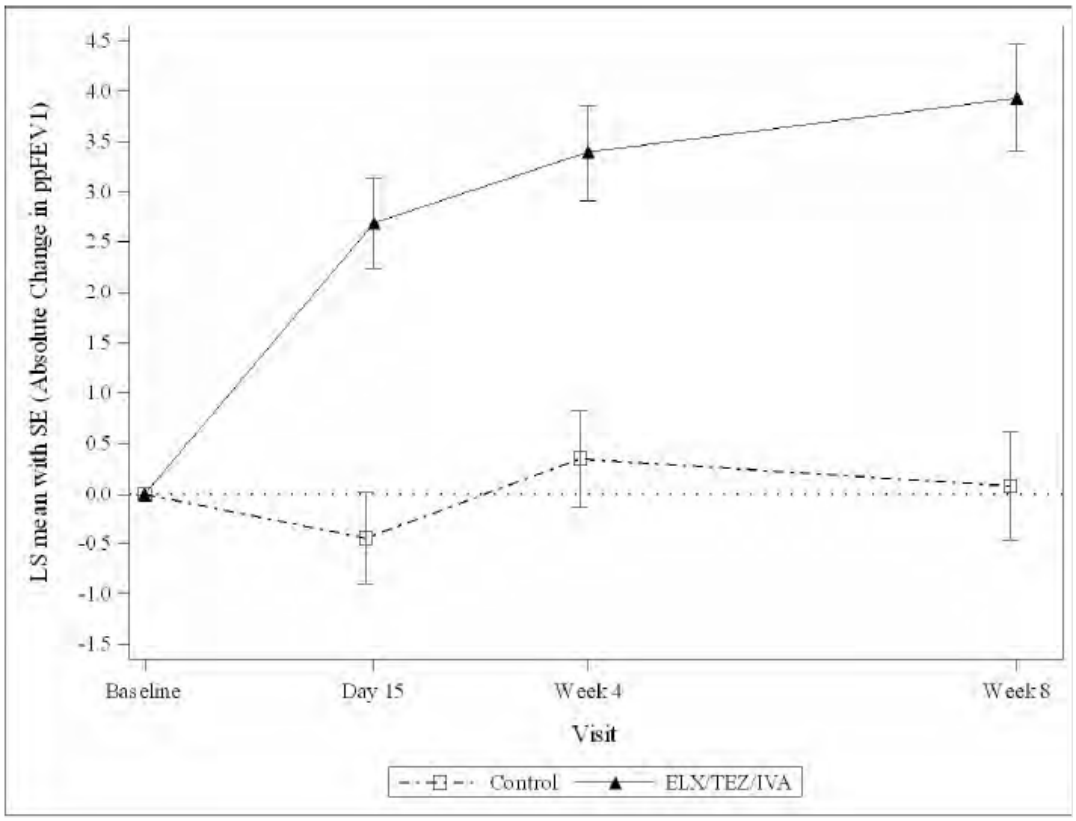
Rapid, robust, and statistically significant improvements in ppFEV1 were demonstrated following ELX/TEZ/IVA treatment, compared to baseline values and compared to the control group (Figure 2 and Table 14).

Study 104 met its primary endpoint; treatment with ELX/TEZ/IVA resulted in a statistically significant improvement in ppFEV1 through Week 8, with a within-group least squares (LS) mean absolute change from baseline of 3.7 percentage points (95% CI: 2.8, 4.6; P<0.0001 [Table 14]).

The between-group absolute change from baseline in ppFEV1 through Week 8 was evaluated as a key secondary endpoint. ELX/TEZ/IVA treatment resulted in a statistically significant improvement in ppFEV1 compared to the control group, with an LS mean treatment difference of 3.5 percentage points (95% CI: 2.2, 4.7; P<0.0001 [Table 14]).

Efficacy data on the IVA and TEZ/IVA comparator groups is presented under subgroup analyses.

Figure 2: Study 104 MMRM Analysis of mean absolute change from baseline in ppFEV1 at each visit up to Week 8.



Source: Study 104 CSR/Figure 14.2.1.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. MMRM included data from all available visits up to Week 8, with treatment, visit, and treatment-by-visit as fixed effects and baseline $ppFEV_1$, baseline SwCl, and comparator group (IVA or TEZ/IVA comparator group) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. Measurements at Day 15 were not included in the estimation of the average treatment effect through Week 8.

Sensitivity Analyses - A prespecified sensitivity analysis was performed using the multiple imputation method, and the results were consistent with the primary analysis. An additional analysis was performed that included spirometry data assessed at home by subjects due to the COVID-19 pandemic, and the results were consistent with the primary analysis.

Sweat Chloride endpoints:

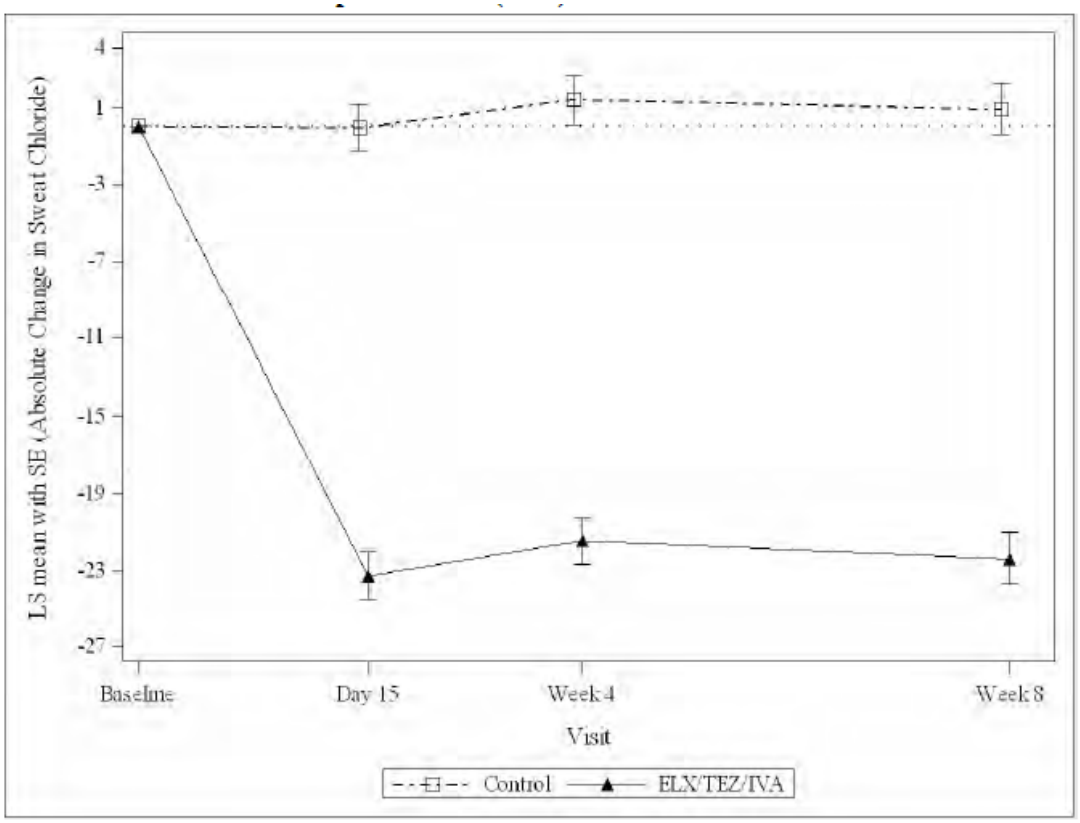
Sweat chloride concentration is an in vivo marker of CFTR function and a sensitive PD marker of CFTR modulation. Rapid, robust, and statistically significant improvements in sweat chloride were

demonstrated following ELX/TEZ/IVA treatment, compared to baseline and compared to the control group (Figure 3 and Table 14).

Within- and between-group changes in sweat chloride through Week 8 were evaluated as key secondary endpoints. Treatment with ELX/TEZ/IVA resulted in a statistically significant improvement in sweat chloride through Week 8, with a within-group LS mean absolute change from baseline of -22.3 mmol/L (95% CI: -24.5, -20.2; P<0.0001 [Table 14]). ELX/TEZ/IVA treatment also resulted in a statistically significant improvement in sweat chloride through Week 8 compared to the control group, with a LS mean treatment difference of -23.1 mmol/L (95% CI: -26.1, -20.1; P<0.0001 [Table 14]).

Efficacy data on the IVA and TEZ/IVA comparator groups is presented under subgroup analyses.

Figure 3: Study 104 MMRM analysis of absolute change from baseline in SwCl at each visit up to week 8 (FAS)



Source: Study 104 CSR/Figure 14.2.2.1

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. MMRM included data from all available visits up to Week 8, with treatment, visit, and treatment-by-visit as fixed effects and baseline $ppFEV_1$, baseline SwCl, and comparator group (IVA or TEZ/IVA comparator group) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

CFQ-R endpoints:

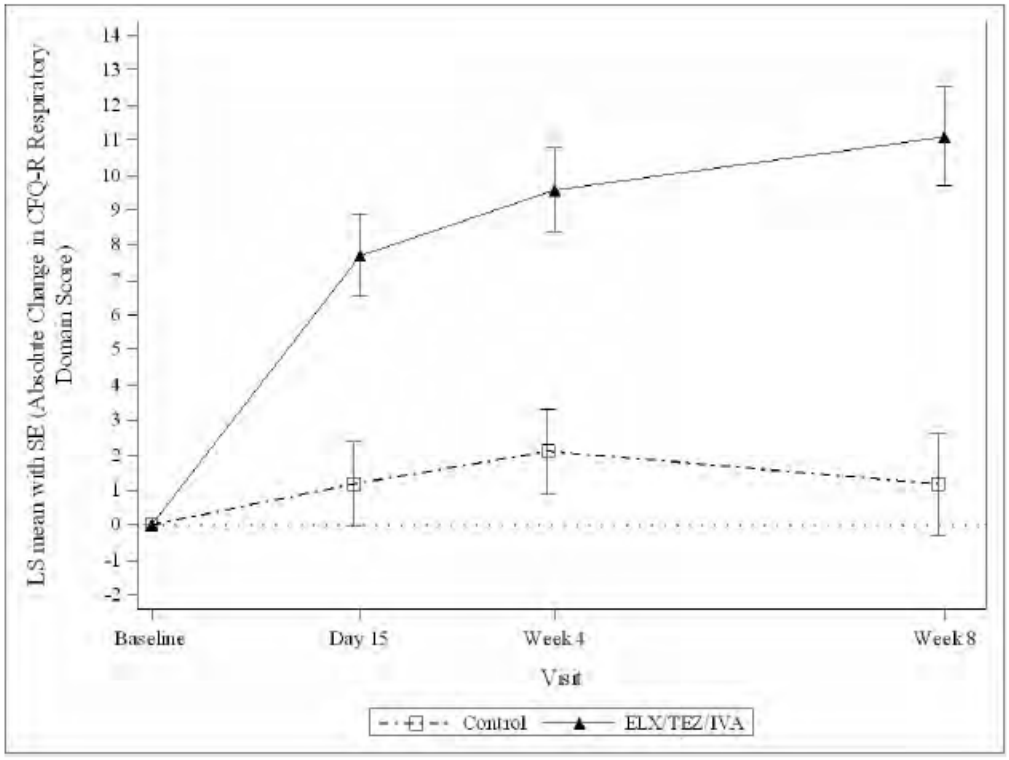
Rapid, robust improvements in respiratory symptoms (CFQ-R RD score) were demonstrated following ELX/TEZ/IVA treatment, compared to baseline and compared to the control group (Figure 4 and Table 14).

Within- and between-group changes in CFQ-R RD score were evaluated as other secondary endpoints. Treatment with ELX/TEZ/IVA resulted in an increase in CFQ-R RD score through Week 8, with a within-group LS mean absolute change from baseline of 10.3 points (95% CI: 8.0, 12.7; nominal P-value <0.0001 [Table 14]). ELX/TEZ/IVA treatment also resulted in an increase in CFQ-R RD score through Week 8 compared to the control group, with an LS mean treatment difference of 8.7 points (95% CI: 5.3, 12.1; nominal P-value <0.0001 [Table 14]). Both changes in CFQ-R RD scores exceeded the MCID of 4 points.

The main analysis was based on pooled CFQ-R RD scores assessed at the clinic and at home. An additional analysis was performed that included only data assessed at the clinic, and the results were consistent with the main analysis.

Efficacy data on the IVA and TEZ/IVA comparator groups is presented under subgroup analyses.

Figure 4: Study 104 MMRM analysis of absolute change from baseline in CFQ-R RD score at each visit up to week 8 (FAS)



Source: Study 104 CSR/Figure 14.2.3.1
CFQ-R: Cystic Fibrosis Questionnaire - Revised; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. MMRM included data from all available visits up to Week 8, with treatment, visit, and treatment-by-visit as fixed effects and baseline $ppFEV_1$, baseline SwCl, and comparator group (IVA or TEZ/IVA comparator group) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. Measurements at Day 15 were not included in the estimation of the average treatment effect through Week 8.

Responder Analyses

Table 15 presents responder analyses by treatment group at the requested thresholds (1.5 and 2.5 percentage points) for ppFEV1; responder analyses for SwCl and CFQ-R RD are also presented.

Table 15: Responder Analysis Through Week 8 for the ELX/TEZ/IVA Group Compared to the Control Group (Study 104 FAS)

Endpoint Response Threshold (Through Week 8)	Control N = 126	ELX/TEZ/IVA N = 132
$ppFEV_1$, n/N1 (%)		
Change ≥1.5 percentage points, n(%)	36/114 (31.6)	66/115 (57.4)
Change ≥2.5 percentage points, n (%)	26/114 (22.8)	57/115 (49.6)
SwCl, n/N1 (%)		
Value <60 mmol/L, n (%)	66/119 (55.5)	100/120 (83.3)
Value <30 mmol/L, n (%)	21/119 (17.6)	60/120 (50.0)
CFQ-R RD score, n/N1 (%)		
Change ≥4 points, n (%)	49/126 (38.9)	83/130 (63.8)

Sources: Adhoc Table 14.2.1.25, Adhoc Table 14.2.2.17, and Adhoc Table 14.2.3.19

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; N1: number of subjects with non-missing value; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

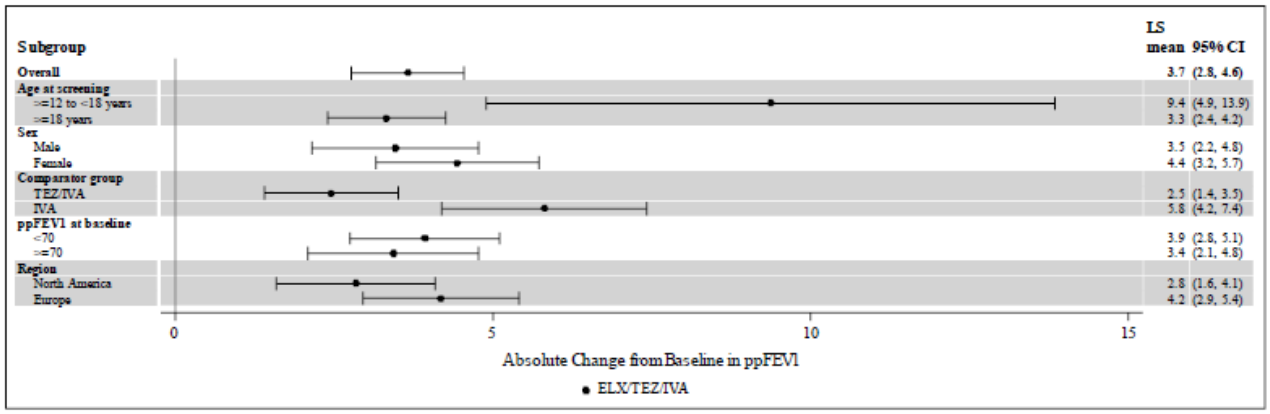
Notes: N1 is the number of subjects with a non-missing value of absolute change through Week 8 in the respective parameter ($ppFEV_1$, SwCl, or CFQ-R RD score).

Ancillary analyses

Subgroup analyses

The results of pre-specified subgroup analyses for ppFEV1 were generally consistent with the result from the primary analysis. Subjects in the ELX/TEZ/IVA group had improvements in ppFEV1 regardless of differences in age, sex, comparator group, baseline lung function, and geographic region (see Figure 5)

Figure 5: Forest plot of LS mean with 95% CI for absolute change from baseline in ppFEV1 through week 8 for the ELX/TEZ/IVA group by subgroup (FAS)



Source: Study 104 CSR/Figure 11-4

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Ad-hoc subgroup analyses per comparator group were performed. A summary of these data is provided in Table 16.

Table 16: study 104 comparator group subgroup analyses (FAS)

	IVA Comparator Group (F/G)		TEZ/IVA Comparator Group (F/RF)	
Statistic	IVA N = 45	ELX/TEZ/IVA N = 50	TEZ/IVA N = 81	ELX/TEZ/IVA N = 82
Primary Endpoint				
Absolute change in **ppFEV$_1$** from baseline through Week 8 for the ELX/TEZ/IVA group (percentage points)				
n	--	42	--	73
LS mean (SE)	--	5.8 (0.8)	--	2.5 (0.5)
95% CI of LS mean	--	(4.2, 7.4)	--	(1.4, 3.5)
Nominal *P* value within treatment	--	<0.0001	--	<0.0001
Key Secondary Endpoints				
Absolute change in **SwCl** from baseline through Week 8 for the ELX/TEZ/IVA group (mmol/L)				
n	--	43	--	77
LS mean (SE)	--	-21.8 (2.0)	--	-23.1 (1.3)
95% CI of LS mean	--	(-25.7, -17.8)	--	(-25.6, -20.6)
Nominal *P* value within treatment	--	<0.0001	--	<0.0001
Absolute change in **ppFEV$_1$** from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group (percentage points)				
n	42	42	72	73
LS mean (SE)	0.1 (0.9)	5.8 (0.8)	0.5 (0.5)	2.5 (0.5)
95% CI of LS mean	(-1.6, 1.7)	(4.2, 7.4)	(-0.5, 1.5)	(1.4, 3.5)
LS mean difference, 95% CI	--	5.8 (3.5, 8.0)	--	2.0 (0.5, 3.4)
Nominal *P* value versus control	--	<0.0001	--	0.0093
Absolute change in **SwCl** from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group (mmol/L)				
n	44	43	75	77
LS mean (SE)	-1.8 (2.0)	-21.8 (2.0)	1.7 (1.3)	-23.1 (1.3)
95% CI of LS mean	(-5.7, 2.2)	(-25.7, -17.8)	(-0.9, 4.3)	(-25.6, -20.6)
LS mean difference, 95% CI	--	-20.0 (-25.4, -14.6)	--	-24.8 (-28.4, -21.2)
Nominal *P* value versus control	--	<0.0001	--	<0.0001
Other Secondary Endpoints				
Absolute change in **CFQ-R RD** score from baseline through Week 8 for the ELX/TEZ/IVA group (points)				
n	--	49	--	81
LS mean (SE)	--	10.2 (1.8)	--	10.4 (1.6)
95% CI of LS mean	--	(6.6, 13.8)	--	(7.2, 13.7)
Nominal *P* value within treatment	--	<0.0001	--	<0.0001
Absolute change in **CFQ-R RD** score from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group (points)				
n	45	49	81	81
LS mean (SE)	1.3 (1.9)	10.2 (1.8)	1.9 (1.6)	10.4 (1.6)
95% CI of LS mean	(-2.5, 5.2)	(6.6, 13.8)	(-1.4, 5.1)	(7.2, 13.7)
LS mean difference, 95% CI	--	8.9 (3.8, 14.0)	--	8.5 (4.0, 13.1)
Nominal *P* value versus control	--	0.0008	--	0.0003

Sources: Study 104 CSR/Table 11-8, Table 11-9, and Table 11-10

CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

Lung function endpoints: FEV1

In the IVA comparator group (F/Gating subjects), the within-group LS mean change from baseline in ppFEV1 through Week 8 in the ELX/TEZ/IVA group was 5.8 percentage points (95% CI: 4.2, 7.4), and the between-group LS mean treatment difference versus IVA was 5.8 percentage points (95% CI: 3.5, 8.0 [Table 16]). In the TEZ/IVA comparator group (F/RF subjects), the within-group LS mean change from baseline in ppFEV1 through Week 8 in the ELX/TEZ/IVA group was 2.5 percentage points (95%

CI: 1.4, 3.5), and the between-group LS mean treatment difference versus TEZ/IVA was 2.0 percentage points (95% CI: 0.5, 3.4 [Table 16]).

Sweat Chloride endpoints:

Subgroup analyses by the comparator group were performed for sweat chloride. In the IVA comparator group (F/Gating subjects), the within-group LS mean change from baseline in sweat chloride through Week 8 in the ELX/TEZ/IVA group was -21.8 mmol/L (95% CI: -25.7, -17.8), and the between-group LS mean treatment difference versus IVA was -20.0 mmol/L (95% CI: -25.4, -14.6 [Table 16]). In the TEZ/IVA comparator group (F/RF subjects), the within-group LS mean change from baseline in sweat chloride through Week 8 in the ELX/TEZ/IVA group was -23.1 mmol/L (95% CI: -25.6, -20.6), and the between-group LS mean treatment difference versus TEZ/IVA was -24.8 mmol/L (95% CI: -28.4, -21.2 [Table 16]).

CFQ-R endpoints:

Subgroup analysis by comparator group was performed for CFQ-R RD score. In the IVA comparator group (F/Gating subjects), the within-group LS mean change from baseline in CFQ-R RD score through Week 8 in the ELX/TEZ/IVA group was 10.2 points (95% CI: 6.6, 13.8), and the between-group LS mean treatment difference versus IVA was 8.9 points (95% CI: 3.8, 14.0 [Table 16]). In the TEZ/IVA comparator group (F/RF subjects), the within-group LS mean change from baseline in CFQ-R RD score through Week 8 in the ELX/TEZ/IVA group was 10.4 points (95% CI: 7.2, 13.7), and the between-group LS mean treatment difference versus TEZ/IVA was 8.5 points (95% CI: 4.0, 13.1 [Table 16]). The treatment difference for both subgroups exceeded the MCID of 4 points.

Responder analyses:

Table 17 presents ppFEV1, SwCl, and CFQ-R RD score responder analyses by comparator and treatment groups using the same thresholds as for the overall population. In all cases, the percentage of responders was higher in the ELX/TEZ/IVA group than in the control group, and the differences between the treatment groups were generally substantial.

Table 17: Responder Analysis Through Week 8 for the ELX/TEZ/IVA Group Compared to the Control Group by Comparator Group (Study 104 FAS)

	IVA Comparator Group		TEZ/IVA Comparator Group	
Endpoint **Response Threshold (Through Week 8)**	**Control N = 45**	**ELX/TEZ/IVA N = 50**	**Control N = 81**	**ELX/TEZ/IVA N = 82**
$ppFEV_1$, n/N1 (%)				
Change ≥1.5 percentage points	11/42 (26.2)	30/42 (71.4)	25/72 (34.7)	36/73 (49.3)
Change ≥2.5 percentage points	9/42 (21.4)	26/42 (61.9)	17/72 (23.6)	31/73 (42.5)
SwCl, n/N1 (%)				
Value <60 mmol/L	33/44 (75.0)	37/43 (86.0)	33/75 (44.0)	63/77 (81.8)
Value <30 mmol/L	7/44 (15.9)	28/43 (65.1)	14/75 (18.7)	32/77 (41.6)
CFQ-R RD score, n/N1 (%)				
Change ≥4 points	20/45 (44.4)	36/49 (73.5)	29/81 (35.8)	47/81 (58.0)

Sources: Adhoc Table 14.2.1.25, Adhoc Table 14.2.2.16, and Adhoc Table 14.2.3.19

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N1: number of subjects with non-missing value; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

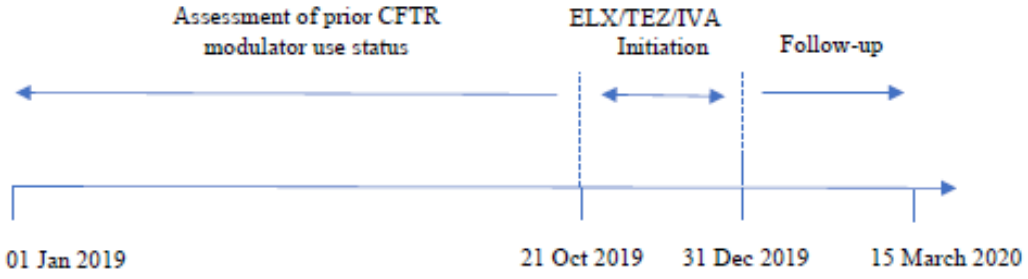
Notes: N1 is the number of subjects with a non-missing value of absolute change through Week 8 in the respective parameter ($ppFEV_1$, SwCl, or CFQ-R RD score).

Real world data from R/G and F/RF patients

During the assessment of the initial MAA of Kaftrio, upon request from CHMP, the MAH provided additional information (ppFEV1 data by genotype for patients who initiated treatment with ELX/TEZ/IVA before 31 Dec 2019) from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) on F/MF, F/F, F/G and F/RF patients treated with VX-445/TEZ/IVA in the post-authorization setting. As CFFPR releases data on an annual basis, data from patients who initiated ELX/TEZ/IVA after 31 Dec 2019 are not yet available.

The same analysis approach described in the initial Kaftrio MAA was used to provide ppFEV1 data by genotype. CF patients who met the following criteria were included in the analysis: (1) had a CFFPR record of initiating treatment with ELX/TEZ/IVA between 21 October 2019 and 31 December 2019, (2) were aged 12 years and older on the date of treatment initiation, (3) had a F/G or F/RF genotype, and (4) had ppFEV1 assessments available both within 90 days before (baseline) and any time after (follow-up) treatment initiation through 15 March 2020.

Figure 6: Patient Population Included in the CFFPR Analyses



Although no changes were made to the analysis period or the inclusion criteria, the number of patients with available data increased compared to the previous analysis, due to ongoing data entry into the CFFPR. In response to CHMP request, the analysis presented ppFEV1 data from 338 patients (157 F/G and 181 F/RF) in comparison to the data from 297 patients (136 F/G and 161 F/RF) presented in the Kaftrio initial MAA. CFQ-R RD data are not routinely collected by the CFFPR and SwCl is rarely entered after CF diagnosis; therefore, no real-world analyses of these endpoints are presented. Analyses of SwCl and CFQ-R RD by-genotype based on Study 104 and Study 110 data are also presented.

Outcomes and Data Analysis

The most recent measurement obtained within 90 days before ELX/TEZ/IVA treatment initiation served as the baseline value for the analysis. The last measurement available in the period following therapy initiation before 15 Mar 2020 served as the follow-up value. The change in ppFEV1 was calculated as a difference between the follow-up and baseline value for each patient. Data were summarized for F/G and F/RF subgroups, and for each CFTR genotype, using summary statistics (mean and standard deviation [SD]).

Patients who initiated ELX/TEZ/IVA treatment in 2019 were followed from the date of ELX/TEZ/IVA treatment initiation through 15 March 2020. Treatment duration was calculated for each patient as the difference between the date of treatment initiation and the date of the last available post-treatment ppFEV1. Recent use of CFTR modulator therapy prior to ELX/TEZ/IVA treatment initiation was defined as being exposed to at least one other CFTR modulator in 2019.

Results

A total of 338 patients with an F/G or F/RF genotype started treatment with ELX/TEZ/IVA between 21 Oct 2019 and 31 Dec 2019 and had lung function measurements available at baseline and follow-up. Their mean treatment duration was 68.6 days. Of these patients, 157 F/G patients had a mean age of 31.8 years and a mean treatment duration of 66.6 days. One hundred eighty-one (181) F/RF patients had a mean age of 39.2 years and a mean treatment duration of 70.3 days. The vast majority of the F/G and F/RF patients included in this analysis were receiving CFTR modulator therapy prior to initiating ELX/TEZ/IVA treatment (96.8% of F/G patients and 87.3% of F/RF patients).

F/G and F/RF Subgroup Results

Mean baseline (SD) ppFEV1 values were 70.0 (25.9) for the F/G patients and 66.8 (24.8) for the F/RF patients, similar to the previous analysis. Results for the F/G and F/RF subgroups were similar to the analysis presented in the initial MAA. ppFEV1 increased by an average of 4.3 percentage points in the F/G group and by an average of 3.0 percentage points in the F/RF group (Table 18).

Table 18: Updated CFFPR Data for F/G and F/RF Patients Who Initiated Treatment With ELX/TEZ/IVA Between 21 Oct 2019 and 31 Dec 2019

Subgroup	Patients n	Pre-ELX/TEZ/IVA $ppFEV_1$ Mean (SD)	Post-ELX/TEZ/IVA $ppFEV_1$ [a] Mean (SD)	Change in $ppFEV_1$ Mean (SD)
F/G	157	70.0 (25.9)	74.3 (24.7)	+4.3 (10.0)
F/RF	181	66.8 (24.8)	69.7 (24.6)	+3.0 (6.1)

Source: data on file from CFFPR

[a] Post-treatment $ppFEV_1$ data examined through 15 Mar 2020

Results by CFTR Genotype

ppFEV1 data from the CFFPR before and after initiation of ELX/TEZ/IVA treatment are presented by genotype in Table 19 (F/G) and Table 20 (F/RF). A total of 16 genotypes were included in the analysis (5 F/G and 11 F/RF), including 7 genotypes (3 F/G and 4 F/RF) that are not included in the analysis of Study 104 data (Question 13) or Study 110 data (Question 9). Due to the limitations of Real World Efficacy data collection, small sample size, and associated variability of subgroups, interpretation of these results has limitations.

Among the 16 CFTR genotypes with data available, an increase in ppFEV1 was observed for 14 genotypes. For the 2 F/G (G551D, R117H) and 7 F/RF (3849+10kbC>T, A455E, 2789+5G>A, 3272-26A>G, D1152H, L206W, and P67L) genotypes with both clinical data and real-world data available, results were consistent between clinical and real-world data, and showed increased ppFEV1 following ELX/TEZ/IVA treatment.

Table 19: CFFPR Data for F/G Patients (By Genotype) Who Initiated Treatment With ELX/TEZ/IVA Between 21 October 2019 and 31 December 2019

Genotype	Patients n	Pre-ELX/TEZ/IVA $ppFEV_1$ Mean (SD)	Post-ELX/TEZ/IVA $ppFEV_1$[a] Mean (SD)	Change in $ppFEV_1$ Mean (SD)
Overall F/G group	157	70.0 (25.9)	74.3 (24.7)	+4.3 (10.0)
G551D	91	68.0 (26.2)	73.2 (25.2)	+5.2 (11.4)
R117H	41	77.8 (21.9)	80.7 (20.7)	+2.9 (6.6)
S549N	8	64.7 (28.3)	65.1 (24.8)	+0.5 (5.8)
S1251N	5	50.3 (19.5)	54.2 (18.9)	+3.8 (3.8)
G1244E	5	51.6 (23.8)	57.8 (27.7)	+6.2 (4.3)

Source: data on file from CFFPR
[a] Post-treatment $ppFEV_1$ data examined through 15 March 2020

Table 20: CFFPR Data for F/RF Patients (By Genotype) Who Initiated Treatment With ELX/TEZ/IVA Between 21 October 2019 and 31 December 2019

Genotype	Patients n	Pre-ELX/TEZ/IVA $ppFEV_1$ Mean (SD)	Post-ELX/TEZ/IVA $ppFEV_1$[a] Mean (SD)	Change in $ppFEV_1$ Mean (SD)
Overall F/RF group	181	66.8 (24.8)	69.7 (24.6)	+3.0 (6.1)
3849+10kbC->T	46	56.3 (26.2)	59.9 (25.5)	+3.6 (6.0)
2789+5G->A	34	70.9 (20.5)	74.0 (20.6)	+3.1 (4.9)
3272-26A->G	21	69.0 (21.5)	72.6 (23.0)	+3.7 (7.7)
D1152H	17	71.2 (20.5)	72.7 (20.5)	+1.5 (7.0)
A455E	11	70.1 (27.0)	76.0 (24.5)	+6.0 (6.2)
L206W	10	88.8 (24.1)	90.3 (23.0)	+1.5 (5.2)
P67L	10	70.9 (21.9)	73.5 (21.9)	+2.6 (5.0)
S945L	10	51.5 (18.1)	53.7 (19.0)	+2.2 (2.5)
711+3A->G	6	80.6 (17.4)	82.3 (16.7)	+1.7 (6.6)
R347H	5	74.6 (18.8)	74.1 (18.6)	-0.5 (5.5)
R117C	5	61.5 (12.9)	57.8 (12.8)	-3.7 (0.4)

Source: data on file from CFFPR
[a] Post-treatment $ppFEV_1$ data examined through 15 March 2020

Among the 2 F/G and 12 F/RF CFTR genotypes that do not have CFTR modulators available in Europe, only 1 genotype had sufficient data for inclusion in the analysis (F/R374H).

Summary of main study

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

Table 21: Summary of efficacy for trial VX18-445-104

Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of Elexacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)			
Study identifier	EudraCT Number: 2018-002835-76		
Design	Randomized, double-blind, active-controlled, multicenter, 12 years and older, CF, heterozygous F/RF or F/G		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 weeks 28 days 28 days safety follow up
Hypothesis	Superiority		
Treatments groups	ELX/TEZ/IVA Group		200 mg ELX/100 mg TEZ/150 mg IVA daily + 150 mg IVA daily for 8 weeks N= 133 (randomized)
	Control Group IVA or TEZ/IVA		IVA: 0 mg ELX/0 mg TEZ/150 mg IVA daily + 150 mg IVA daily for 8 weeks TEZ/IVA: 0 mg ELX/100 mg TEZ/150mg IVA daily + 150 mg IVA daily for 8 weeks N=126 (randomized)
Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change in ppFEV1 from baseline through week 8 for the ELX/TEZ/IVA group
	Key Secondary	SwCL	Absolute change in SwCL from baseline through week 8 for the ELX/TEZ/IVA group
	Key Secondary	ppFEV1	Absolute change in ppFEV1 from baseline through week 8 for the ELX/TEZ/IVA group compared to the control group
	Key Secondary	SwCL	Absolute change in SwCL from baseline through week 8 for the ELX/TEZ/IVA group compared to the control group
	Secondary	CFQ-R RD	Absolute change in CFQ-R RD score from baseline through week 8 for the ELX/TEZ/IVA group
	Secondary	CFQ-R RD	Absolute change in CFQ-R RD score from baseline through week 8 for the ELX/TEZ/IVA group compared to the control group
Database lock	30 June 2020		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug in the Treatment Period – 8 weeks		
Descriptive statistics and estimate variability	Treatment group	Control Group	ELX/TEZ/IVA
	Number of subject	126	132
	LS mean ppFEV1	0.2	3.7
	95% CI of LS mean	(-0.7, 1.1)	(2.8, 4.6)
	LS mean SwCl	0.7	-22.3
	95% CI of LS mean	(-1.4, 2.8)	(-24.5, -20.2)
	LS mean CFQ-R	1.6	10.3

	95% CI of LS mean	(-0.8, 4.1)	(8.0, 12.7)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	ELX/TEZ/IVA vs Control
		LS mean ppFEV1	3.5
		95% CI	2.2, 4.7
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	ELX/TEZ/IVA vs Control
		LS mean difference SwCl	-23.1
		95% CI	-26.1, -20.1
		P-value	<0.0001
	Secondary endpoint	Comparison groups	ELX/TEZ/IVA vs Control
		LS mean difference CFQ-R	8.7
		95% CI	5.3, 12.1
		P-value	<0.0001
Notes	All primary and key secondary endpoints were controlled for multiplicity and were statistically significant in the framework of the testing hierarchy. Comparison to the two separate control groups of IVA and TEZ/IVA was not prespecified. These analyses were ad-hoc.		
Analysis description	**Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial within-group effect for ELX/TEZ/IVA. *Compared to IVA:* The between-group data show a beneficial change in ppFEV1 of 5.8 percentage point (95% CI: 3.5, 8.0; nominal p<0.0001), in SwCL of -20.0 mmol/L (95% CI: -25.4, -14.6; nominal p<0.0001) and in CFQ-RD of 8.9 points (95% CI: 3.8, 14.0; nominal p=0.0008). *Compared to TEZ/IVA:* The between-group data show a beneficial change in ppFEV1 of 2.0 percentage point (95% CI: 1.4, 3.5; nominal p=0.0093), in SwCL of -24.8 mmol/L (95% CI: -28.4, -21.2; nominal p<0.0001) and in CFQ-RD of 8.5 points (95% CI: 4.0, 13.1; nominal p=0.0003).		

Clinical studies in special populations

The trial included adolescents and adults. Subgroup analyses of the primary endpoint were performed using a model similar to that for the primary analysis. Subgroup analyses showed consistent changes in ppFEV1 regardless of age, sex, baseline lung function and geographic region.

Study 104 excluded pregnant and lactating women and also excluded subjects with a history of any illness or condition that could confound study results or pose an additional safety risk (e.g. clinically significant hepatic cirrhosis with or without portal hypertension).

The studies did include a small number of patients aged 60/65 years and older, as the maximum age is 72.7 in the control group and 69.8 in the ELX/TEZ/IVA group. Nineteen patients over the age of 60 years were recruited to the study. Six patients over the age of 65 years were recruited to the study and of these 2 were treated with Kaftrio. Of these only 1 patient had post-baseline percent predicted forced expiratory volume in 1 second (ppFEV1) data available. The baseline (Day 1) ppFEV1 value was 85.7% and the average through Week 8 of Study 104 was 85.8%.

Study 110 results are preliminary; this study is ongoing. The study was not powered for the subgroup analyses described below (Tables 22 through 27).

In long-term safety and efficacy Study 110, 6 subjects ≥65 years were treated with ELX/TEZ/IVA. The data for these subjects are included in

Table 22.

Table 22: Efficacy summary statistics for Subjects at least 65 years of age treated with ELX/TEZ/IVA in study 110 (OL FAS)

Visit Statistic	ppFEV$_1$ (percentage points)	SwCl (mmol/L)	CFQ-R RD Score (points)
Baseline (Study 104)			
n	6	6	6
Mean (SD)	62.7 (19.5)	60.6 (33.8)	84.3 (11.9)
Absolute change from baseline through Study 110 Week 24			
n	3	5	6
Mean (SD)	4.2 (5.6)	-21.0 (22.9)	3.6 (13.7)

Source: Ad Hoc Table 14.2.8.1

CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride

Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of Study 104. ppFEV$_1$ summary includes spirometry data obtained in clinic only. CFQ-R RD score summary includes both in-clinic and home-assessed data.

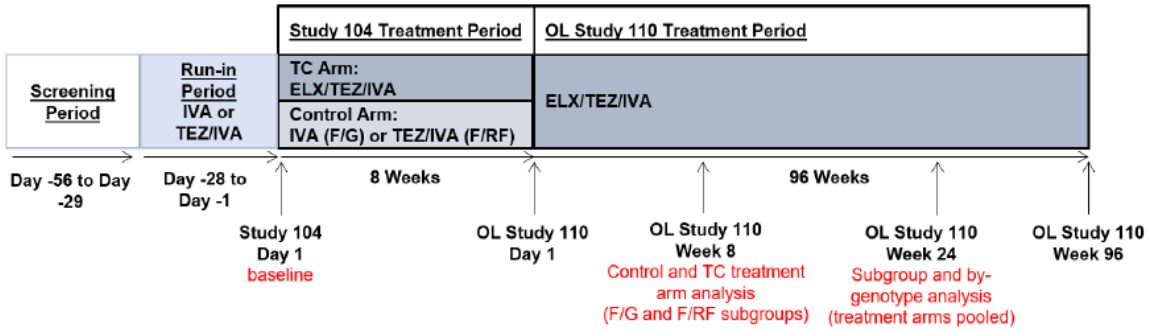
Supportive studies

Study 110

Study 110 is a Phase 3, open-label study evaluating the long-term safety and efficacy of VX-445 combination therapy in subjects with cystic fibrosis who are heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF Genotypes)

The MAH has performed 2 different analyses with data from control patients from Study 104, who moved to Kaftrio in the OLE Study 110. Data up to 14 Dec 2020 was included. Figure 7 below summarises both analyses based on protocol v1.0.

Figure 7: Schematic of Study 110 Design and Analysis



ELX: elexacaftor; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a second allele that results in residual function; IVA: ivacaftor; OL: open label; TEZ: tezacaftor

The first analysis consisted of F/G and F/RF subgroup data analysed through Week 8, to facilitate comparison with results from Study 104.

As of 14 Dec 2020, 251 subjects had received at least one dose of ELX/TEZ/IVA in Study 110 and were included in the OL Full Analysis Set (OL FAS), including 121 subjects who received control treatment in

Study 104 and 130 subjects who received ELX/TEZ/IVA in Study 104. There were 92 F/G subjects and 159 F/RF subjects in the OL FAS.

For study 110, the results for both control group and Kaftrio group at open-label week 8 are displayed in Table 23 (FEV1), Table 24 (sweat chloride) and Table 25 (CFQ-R Respiratory Domain Score) and broken down per F/RF and F/G category. Please note that Study 110 results are preliminary; this study is ongoing. The study was not powered for the subgroup analyses described below (Table 23 to Table 28). For all patients, the baseline was taken to be their Study 104 baseline, which given the relatively short duration of Study 104 can be accepted. The inclusion of Week 8 open-label outcomes from the Kaftrio group of Study 104 is useful for comparative purposes.

Table 23: Summary of Absolute Change from Parent Study Baseline in ppFEV1 (percentage points) through Open label Week 8 by Parent Study Treatment Group (Study 110 OL FAS)

		F/G IVA Comparator Group		F/RF TEZ/IVA Comparator Group		Overall	
Visit	Statistics	IVA→ ELX/TEZ/IVA N = 43	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 49	TEZ/IVA→ ELX/TEZ/IVA N = 78	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 81	Control→ ELX/TEZ/IVA N = 121	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 130
Absolute change through OL Study 110 Week 8							
	n	32	33	52	48	84	81
	Mean (SD)	4.7 (7.0)	4.8 (6.4)	2.9 (5.0)	3.0 (5.3)	3.6 (5.9)	3.7 (5.8)

Source: Study 110 Adhoc Table 14.2.1.5

ELX: elexacaftor; FAS: Full Analysis Set; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a second allele that results in residual function; IVA: ivacaftor; N: size of sample; n: size of subsample; OL: open label; 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 (Study 104). Through OL Week 8 is defined as the average of OL Week 4 and OL Week 8.

Table 24: Summary of Absolute Change from Parent Study Baseline in Sweat Chloride (mmol/L) through Open-label Week 8 by Parent Study Treatment Group (Study 110 OL FAS)

		F/G IVA Comparator Group		F/RF TEZ/IVA Comparator Group		Overall	
Visit	Statistics	IVA→ ELX/TEZ/IVA N = 43	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 49	TEZ/IVA→ ELX/TEZ/IVA N = 78	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 81	Control→ ELX/TEZ/IVA N = 121	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 130
Absolute change through OL Study 110 Week 8							
	n	36	40	62	63	98	103
	Mean (SD)	-17.6 (13.4)	-20.5 (20.1)	-26.2 (15.8)	-23.7 (18.1)	-23.0 (15.5)	-22.5 (18.9)

Source: Study 110 Adhoc Table 14.2.2.4

ELX: elexacaftor; FAS: Full Analysis Set; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a second allele that results in residual function; IVA: ivacaftor; N: size of sample; n: size of subsample; OL: open label; 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 (Study 104). Through OL Week 8 is defined as the average of OL Day 15, OL Week 4 and OL Week 8.

Table 25: Summary of Absolute Change from Parent Study Baseline in CFQ-R Respiratory Domain Score through Open-label Week 8 by Parent Study Treatment Group (Study 110 OL FAS)

Table 13 Summary of Absolute Change from Parent Study Baseline in CFQ-R Respiratory Domain Score through Open-label Week 8 by Parent Study Treatment Group (Study 110 OL FAS)

		F/G IVA Comparator Group		F/RF TEZ/IVA Comparator Group		Overall	
Visit	Statistics	IVA→ ELX/TEZ/IVA N = 43	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 49	TEZ/IVA→ ELX/TEZ/IVA N = 78	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 81	Control→ ELX/TEZ/IVA N = 121	ELX/TEZ/IVA→ ELX/TEZ/IVA N = 130
Absolute change through OL Study 110 Week 8							
	n	43	47	73	78	116	125
	Mean (SD)	10.7 (14.9)	10.3 (14.0)	9.1 (12.0)	10.3 (16.1)	9.7 (13.1)	10.3 (15.3)

Source: Study 110 Adhoc Table 14.2.6.5

ELX: elexacaftor; FAS: Full Analysis Set; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a second allele that results in residual function; IVA: ivacaftor; N: size of sample; n: size of subsample; OL: open label; TEZ: tezacaftor

Notes: CFQ-R 'Children Ages 12 and 13' Versions and 'Adolescents and Adults' Versions were pooled. 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 (Study 104). Through OL Week 8 is defined as the average of OL Week 4 and OL Week 8.

The second analysis consisted of genotype-level data through Week 24 of the OLE, with data from the Study 104 control and ELX/TEZ/IVA treatment arms pooled to maximize the sample size for each genotype.

The second analysis tries to broaden the genotype level dataset with respect to efficacy (albeit with open label data), given the rareness of many of the non F mutations, and because half of the subjects recruited in Study 104 did not receive Kaftrio. To optimise the dataset, and minimise the effect of missing data, the MAH has pooled patients from both the control and Kaftrio arms in Study 104 (n=251) and has selected a Study 110 week 24 cut off. Again, for all patients the baseline was taken to be their Study 104 baseline, which given the fairly short duration of Study 104 can be accepted for the purpose of this analysis.

Only CFTR genotypes with 5 or more evaluable subjects were considered suitable for the analysis; data from those genotypes represented less than 5 times were considered not reliable enough to be useful. Table 26 lists 2 F/G genotypes, and Table 27 lists 7 F/RF genotypes and a summary of absolute change from Study 104 baseline in ppFEV1, SwCl, and CFQ- R RD through open label week 24 is shown for each.

Table 26: F/G: Summary of Absolute Change from Parent Study Baseline in ppFEV1, Sweat Chloride, and CFQ-R RD Through Open Label Week 24 By Genotype (Study 110 OL FAS)

	ELX/TEZ/IVA N = 251		
	$ppFEV_1$ (percentage points)	**SwCl (mmol/L)**	**CFQ-R RD (points)**
F/G subgroup			
n	76	86	92
mean (SD)	5.5 (7.4)	-19.0 (17.8)	10.5 (13.8)
F/G551D			
n	48	54	59
mean (SD)	7.7 (7.3)	-23.3 (19.5)	10.8 (10.3)
F/R117H			
n	11	15	15
mean (SD)	1.3 (6.4)	-12.0 (9.7)	8.1 (20.5)

Source: Study 110 Adhoc Tables 14.2.1.6, 14.2.1.7, 14.2.2.5, 14.2.2.6, 14.2.6.6, 14.2.6.7

CFQ-R RD: Cystic Fibrosis Questionnaire – Revised respiratory domain; ELX: elexacaftor; IVA: ivacaftor; n: number of subjects with non-missing parameter in the corresponding genotype group; OL FAS: Open-label Full Analysis Set; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: A genotype is included when there are ≥5 subjects with at least one non-missing $ppFEV_1$ at OL Week 4, OL Week 8, OL Week 16 or OL Week 24 Visits. 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. Table is sorted by number of subjects in descending order.

Table 27: F/RF: Summary of Absolute Change from Parent Study Baseline in ppFEV1, Sweat Chloride, and CFQ-R RD Through Open Label Week 24 by Genotype (Study 110 OL FAS)

	ELX/TEZ/IVA N = 251		
	ppFEV$_1$ (percentage points)	SwCl (mmol/L)	CFQ-R RD (points)
F/RF subgroup			
n	129	143	157
mean (SD)	3.2 (5.4)	-26.4 (17.3)	9.6 (14.1)
F/3849+10kbC>T			
n	31	33	37
mean (SD)	3.8 (5.6)	-17.5 (9.7)	15.7 (15.3)
F/2789+5G>A			
n	29	32	34
mean (SD)	5.1 (5.3)	-39.5 (13.0)	9.0 (13.6)
F/A455E			
n	21	20	21
mean (SD)	3.3 (7.0)	-43.9 (7.4)	9.2 (11.0)
F508del/3272-26A>G			
n	16	18	19
mean (SD)	1.6 (4.4)	-33.3 (14.9)	2.7 (11.6)
F508del/D1152H			
n	7	9	10
mean (SD)	0.7 (3.4)	-1.0 (9.0)	8.8 (17.1)
F508del/L206W			
n	6	5	6
mean (SD)	1.2 (6.5)	-15.8 (10.8)	8.3 (23.3)
F508del/P67L			
n	6	8	10
mean (SD)	2.5 (2.7)	-11.0 (8.3)	9.4 (8.7)

Source: Study 110 Adhoc Tables 14.2.1.6, 14.2.1.7, 14.2.2.5, 14.2.2.6, 14.2.6.6, 14.2.6.7

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

Notes: A genotype is included when there are ≥5 subjects with at least one non-missing ppFEV$_1$ at OL Week 4, OL Week 8, OL Week 16 or OL Week 24 Visits. 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. Table is sorted by number of subjects in descending order.

Studies included in the initial Kaftrio procedure (study 102, 103 and 105)

ELX/TEZ/IVA efficacy in patients with F/MF and F/F genotypes was demonstrated in Studies 102 and 103, respectively. Treatment with ELX/TEZ/IVA resulted in rapid, robust, clinically meaningful, and statistically significant improvements in all primary and key secondary efficacy and pharmacodynamics (PD) endpoints in Study 102 (Table 28) and Study 103 (Table 29).

A detailed discussion of Study 102 and 103 efficacy results is included in initial MAA.

Table 28: Study 102 (F/MF subjects): primary and key secondary efficacy analyses

Analysis	Statistic	Placebo N = 203	ELX/TEZ/IVA N = 200
Primary Endpoint[a]			
Absolute change from baseline in $ppFEV_1$ through Week 24 (percentage points)	n	203	196
	LS mean (SE)	-0.4 (0.5)	13.9 (0.6)
	95% CI of LS mean	(-1.5, 0.7)	(12.8, 15.0)
	LS mean difference, 95% CI	--	**14.3 (12.7, 15.8)**
	P value versus placebo	--	<0.0001
Select Key Secondary Endpoints[b]			
Number of PEx through Week 24	Number of subjects with events, n (%)	76 (37.4)	31 (15.5)
	Number of events	113	41
	Estimated event rate per year	0.98	0.37
	Rate ratio, 95% CI	--	**0.37 (0.25, 0.55)**
	P value versus placebo	--	<0.0001
Absolute change from baseline in SwCl through Week 24 (mmol/L)	n	201	199
	LS mean (SE)	-0.4 (0.9)	-42.2 (0.9)
	95% CI of LS mean	(-2.2, 1.4)	(-44.0, -40.4)
	LS mean difference, 95% CI	--	**-41.8 (-44.4, -39.3)**
	P value versus placebo	--	<0.0001
Absolute change from baseline in CFQ-R RD score through Week 24 (points)	n	203	200
	LS mean (SE)	-2.7 (1.0)	17.5 (1.0)
	95% CI of LS mean	(-4.6, -0.8)	(15.6, 19.5)
	LS mean difference, 95% CI	--	**20.2 (17.5, 23.0)**
	P value versus placebo	--	<0.0001
Absolute change from baseline in BMI at Week 24 (kg/m^2)	n	202	198
	LS mean (SE)	0.09 (0.07)	1.13 (0.07)
	95% CI of LS mean	(-0.05, 0.22)	(0.99, 1.26)
	LS mean difference, 95% CI	--	**1.04 (0.85, 1.23)**
	P value versus placebo	--	<0.0001

Source: Initial MAA Module 2.7.3/Table 9

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; ELX: elexacaftor; F/MF: heterozygous for *F508del* and an MF mutation; FAS: Full Analysis Set; 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: Analyses were based on the FAS. FAS was defined as all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug.

[a] European protocol.

[b] European and global protocols.

Table 29: Study 103 (F/F subjects): primary and key secondary efficacy analyses

Analysis	Statistic	TEZ/IVA N = 52	ELX/TEZ/IVA N = 55
Primary Endpoint			
Absolute change from baseline in $ppFEV_1$ at Week 4 (percentage points)	n	49	53
	LS mean (SE)	0.4 (0.9)	10.4 (0.9)
	95% CI of LS mean	(-1.4, 2.3)	(8.6, 12.2)
	LS mean difference, 95% CI	--	**10.0 (7.4, 12.6)**
	P value versus TEZ/IVA	--	<0.0001
Key Secondary Endpoints			
Absolute change from baseline in SwCl at Week 4 (mmol/L)	n	48	54
	LS mean (SE)	1.7 (1.8)	-43.4 (1.7)
	95% CI of LS mean	(-1.9, 5.3)	(-46.9, -40.0)
	LS mean difference, 95% CI	--	**-45.1 (-50.1, -40.1)**
	P value versus TEZ/IVA	--	<0.0001
Absolute change from baseline in CFQ-R RD score at Week 4 (points)	n	52	55
	LS mean (SE)	-1.4 (2.0)	16.0 (2.0)
	95% CI of LS mean	(-5.4, 2.6)	(12.1, 19.9)
	LS mean difference, 95% CI	--	**17.4 (11.8, 23.0)**
	P value versus TEZ/IVA	--	<0.0001

Source: Initial MAA Module 2.7.3/Table 12

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; ELX: elexacaftor; F/F: *F508del* on both alleles; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Analyses were based on the FAS. FAS was defined as all randomized subjects who carry the intended *CFTR* allele and received at least 1 dose of study drug.

Table 30 summarizes the ELX/TEZ/IVA treatment effects observed in the Phase 3 studies (Studies 102, 103, and 104) by CFTR genotype group. For context, the treatment effects of previously approved CFTR modulators IVA and TEZ/IVA are also presented in Table 30. Due to the IVA and TEZ/IVA Run-in Period in Study 104, these treatment effects should be considered compared to F/MF subjects in Study 102 and F/F subjects in Study 103. Overall, the totality of the Phase 3 results demonstrates clinically meaningful improvements following ELX/TEZ/IVA treatment across all genotype groups, including F/RF.

Table 30: ELX/TEZ/IVA, TEZ/IVA, and IVA Treatment Effects by CFTR Genotype Group

CFTRm Program Study Number – *CFTR* Genotype (Subgroup)	Analysis	ppFEV$_1$ (Percentage Points)	SwCl (mmol/L)	CFQ-R RD (Points)
F/MF Subjects				
ELX/TEZ/IVA				
Study 445-102	LS mean difference (95% CI) versus *placebo* through Week 24	14.3 (12.7, 15.8)	-41.8 (-44.4, -39.3)	20.2 (17.5, 23.0)
F/F Subjects				
ELX/TEZ/IVA				
Study 445-103	LS mean difference (95% CI) versus *TEZ/IVA* at Week 4	10.0 (7.4, 12.6)	-45.1 (-50.1, -40.1)	17.4 (11.8, 23.0)
TEZ/IVA				
Study 661-106	LS mean difference (95% CI) versus *placebo* through Week 24	4.0 (3.1, 4.8)	-10.1 (-11.4, -8.8)	5.1 (3.2, 7.0)
F/G Subjects				
ELX/TEZ/IVA				
Study 445-104 (IVA comparator group)	LS mean difference (95% CI) versus *IVA* through Week 8	5.8 (3.5, 8.0)	-20.0 (-25.4, -14.6)	8.9 (3.8, 14.0)
IVA				
Study 770-102 – *G551D*	LS mean difference (95% CI) versus *placebo* through Week 24	10.6 (8.6, 12.6)	-47.9 (-51.3, -44.5)	8.1 (4.7, 11.4)
Study 770-111 - Non-*G551D* Gating	LS mean difference (95% CI) versus *placebo* through Week 8	10.7 (7.3, 14.1)	-49.2 (-57.0, -41.4)	9.6 (4.5, 14.7)
Study 770-110- *R117H* (Subjects ≥18 years)	LS mean difference (95% CI) versus *placebo* through Week 24	5.0 (1.1, 8.8)	-21.9 (-26.5, -17.3)	12.6 (5.0, 20.3)
F/RF Subjects				
ELX/TEZ/IVA				
Study 445-104 (TEZ/IVA comparator group)	LS mean difference (95% CI) versus *TEZ/IVA* through Week 8	2.0 (0.5, 3.4)	-24.8 (-28.4, -21.2)	8.5 (4.0, 13.1)
TEZ/IVA				
Study 661-108	LS mean difference (95% CI) versus *placebo* at average of Week 4 and Week 8	6.8 (5.7, 7.8)	-9.5 (-11.7, -7.3)	11.1 (8.7, 13.6)

Sources: Initial Kaftrio MAA Module 2.5/Table 10 and Table 11; Study 445-104 Module 2.7.3/Table 8; Study 770-102 CSR/Table 2-2; Study 770-110 Tables 14.2.1.2.4, 14.2.2.2.3, and 14.2.3.2.3, Study 770-111 CSR/Table 2-2; Study 661-106 CSR/Table 11-2 (ppFEV$_1$), Table 11-9 (SwCl), and Table 11-7 (CFQ-R RD); Study 661-108/Table 11-3 (ppFEV$_1$), Table 11-7 (SwCl), and Table 11-5 (CFQ-R RD)

CFTR: cystic fibrosis transmembrane conductance regulator gene; CFQ-R RD: Cystic Fibrosis Questionnaire – Revised respiratory domain; ELX: elexacaftor; F/F: homozygous for *F508del*; F/G: heterozygous for *F508del* and a second mutation that results in a gating defect; F/MF: heterozygous for *F508del* and minimal function mutation; F/RF: heterozygous for F508del and a second allele that function; IVA: ivacaftor; LS: least square; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

2.4.2. Discussion on clinical efficacy

Kaftrio is a CFTR modulator therapy that includes the active substances elexacaftor, tezacaftor and ivacaftor. Kaftrio was approved in August 2020 in F/MF and F/F patient populations based on study results in F/MF (study 102) and F/F (study 103) CF patients. Long-term data from these F/MF and F/F populations were provided in study 105.

In the current procedure, data in the F/RF and F/G population are provided (study 104) and the MAH applies again for the broad F/any indication as follows:

"Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene."

Design and conduct of clinical studies

Efficacy and safety of Kaftrio (ELX/TEZ/IVA) have been evaluated in 4 studies in CF patients aged 12 years and older. The studies 102 (F/MF), 103 (F/F) and 105 (long-term) were assessed and discussed during the initial MAA and led to the approval of Kaftrio in F/F and F/MF CF patients. The current extension of indication is based on the results of study 104, a randomised, double-blind, controlled

multicentre study. Study 104 was designed to provide for prescribers and patients a quantification of the magnitude of clinical benefit derived from VX-445/TEZ/IVA in F/G and F/RF patients, and not as a pivotal study.

Comparator

The comparators used are Kalydeco (IVA) in the F/G patients and Symkevi (TEZ/IVA) in the F/RF patients. These comparators are considered acceptable by CHMP. Similar to the pivotal studies, and as was outlined as a deficiency in the Kaftrio approval (not addressing the requirements in EMA's Guideline on the clinical development of fixed combination medicinal products), only the possibility of ELX in combination with both TEZ and IVA has been evaluated in Study 104. The need for the TEZ component in both F/G and F/RF is not clear and is particularly relevant for F/Gs where the addition of TEZ has previously been shown in Study 109 to not provide additional response over IVA alone. However when the totality of the evidence for Kaftrio was considered, this was not pursued in relation to F/MF and F/F and will also not be pursued in this assessment focussed on F/G and F/RF genotypes.

Duration

The duration of the treatment period in study 104 was 8 weeks. Such a treatment period is not in line with the Cystic fibrosis EU guideline and important parameters such as exacerbations, and BMI cannot be reliably measured. However, the sustained effect of ELX/TEZ/IVA has been studied in F/G and F/RF patients in study 110 and in F/F and F/MF patients the long-term open-label extension study 105. Furthermore, 251 patients enrolled in the open-label study 110 (out of 253 patients who completed Study 104), and will provide long term safety and efficacy data for F/G and F/RF patients for up to 96 weeks, albeit uncontrolled. Taking this into account, the current 8-week duration was considered acceptable by CHMP to evaluate the efficacy and safety parameters of ELX/TEZ/IVA in the F/G and F/RF populations.

Inclusion and exclusion criteria

In general, the inclusion and exclusion criteria were very similar to the criteria for studies 102 and 103 from the Kaftrio initial MAA. In these studies, the patient population targeted in terms of disease severity was moderate to severe disease, which is considered to represent the patients most likely to demonstrate improvement. Also, for study 104 the CF diagnosis was confirmed by the investigator and no longer a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis was required. Considering that all the subjects will have two disease-causing mutations, the minimal sweat chloride value is not a prerequisite for the CF diagnosis. The inclusion and exclusion criteria are considered acceptable.

Patients with an F/G or F/RF were eligible when they were treated in a region where their genotype and age group were approved indications for treatment with IVA and/or TEZ/IVA. Considering that the indication of Kalydeco and Symkevi differ between the US and EU it could occur that patients would be included in the trial while their mutation is not included in the European indications. Considering the eligibility (see Table 3), this was the case for two gating mutations and 12 residual function mutations. However, of these, only one (*R347H patients*) has been recruited in the trials (see results genotypes). Therefore, the population included in the 104 trial is considered representative for the Kalydeco and Symkevi approved European populations.

It is noted that the mean age of the patient population recruited is older than that recruited in the 2 pivotal trials of ELX/TEZ/IVA: the mean age in Studies 102 and 103 was in the mid-late 20s, whereas for study 104 there was a mean age of 37.7 years, with a mean age of 37.6 years in the control group, and 37.7 years in the treatment group. Overall, 9.3% of patients fell in the 12 to 18 year age bracket; slightly more in the treatment group (11.4%) than in the control group (7.1%). Both genotype-based comparator groups in Study 104 were older, on average, than the gating and F/RF subjects in previous Vertex CF programs. The minimal and maximum ages included in the studies are

relatively similar. It is acknowledged that the older age of the F/RF subjects is caused by the different natural history for these patients. Thus, if the patients had a milder course, as could be hypothesised on their higher mean age and still reasonably well preserved pulmonary function, the observed gain ppFEV1 can even be considered more relevant.

The median weight, height and body mass Index (BMI) for both treatment and control groups were matched, and the overall mean BMI was 24.06 (range 15.81 to 44.36). In terms of previous or baseline treatments, again the groups are broadly similar. Over half of the patients had used dornase alpha (52.3%) or any bronchodilator (86.8%). Other common previous or baseline treatments included azithromycin (44.2%), inhaled antibiotic (40.7%), and inhaled hypertonic saline (43%). Overall the 2 groups were balanced for all of these prior therapies; any of the small differences are unlikely to be meaningful. For most of the concomitant medication, the use was similar between the control and ELX/TEZ/IVA groups in each of the two separate patients populations. However, an imbalance was seen for Azithromycin in the F/G population (55.6% in the IVA group and 34.0% in the ELX/TEZ/IVA group). The same imbalance is also seen for the prior medication. Considering all other baseline parameters and concomitant medication are well balanced between the IVA and ELX/TEZ/IVA group, it is unlikely that this imbalance is caused by a difference in CF severity between these groups.

With regard to prior medication, upon request by CHMP, the MAH provided the percentage of the subjects that received TEZ or TEZ/IVA prior to the study. In general, less F/RF patients were on prior modulator therapy compared to F/G patients. However, in the separate patient populations, the prior modulator use is balanced between placebo and the active treatment group.

Mean FEV1, sweat chloride and CFQ-R scores were balanced in both treatment groups. Overall mean baseline ppFEV1 was 67.6%, sweat chloride was 58mmol/L, and CFQ-R RD was 76.9. These all reflect a slightly less severely affected patient population than the baseline F/MF and F/F populations recruited to Studies 102 and 103 respectively, which is not unexpected.

Furthermore, some patients are included with baseline FEV1 values below <40 and over 90. It is anticipated that the inclusion criterion pertaining to screening ppFEV1 was met in all enrolled subjects in Study 104, but the ppFEV1 decreased at their baseline study visit.

When viewing the baseline SwCL characteristics, it is noticed that the included populations might have a relative milder CF severity. Especially the SwCl values are relatively low in study 104. These baseline levels are measured after the 4-week TEZ/IVA or IVA run-in period. After these 4 weeks an effect of TEZ/IVA is indeed expected, which explains that these lower SwCL levels are comparable to SwCl values after IVA or TEZ/IVA treatment in the F/G and F/RF patients in registration studies for Kalydeco and Symkevi, respectively. Overall, a total of 59.3% of subjects had a positive test for Pseudomonas aeruginosa within 2 years of screening, and this rate was very similar in both treatment and control groups.

In additional tables provided comparing F/G patients versus F/RF patients in terms of baseline demographics and disease metrics, overall the F/G patients were somewhat younger than the F/RF patients (mean age of 32.2 years v 40.8 years for the F/RF patients), and a higher proportion were male (58.9% of the F/G patients were male versus 45.4% of F/RF patients). Mean baseline FEV1 was comparable for both F/G and F/RF (67.0 V 67.9), as was CFQ–RD scores, however, the F/G group had a lower baseline SwCl of 49.3mmol/L V 63.0 mmol/L in the F/RFs. The proportion of G versus RF was, however, balanced in both the control and treatment arms.

Of note, a higher number of patients overall were recruited from the F/RF genotype- 163 patients versus 95 patients with a F/G genotype. Overall 63.2% (approx. 2/3) had a RF mutation and therefore a run-in with TEZ/IVA (and TEZ/IVA as the control) while 36.8% (approx. 1/3) had a G mutation and had a run-in with IVA (and IVA as the control). The proportion of RF versus G was however balanced in

both the control and treatment arms. The 10 different gating mutations in the trial are included in the Kalydeco product information in the EU. For the genotypes with a residual function mutation (TEZ/IVA comparator group), the *R347H* genotype is only included in the US label, but only 1 patient with this mutation is included in the study. The fact that distribution of the included mutations is unequal (e.g. over half of the IVA comparator group has the G551D mutation) is related to the prevalence of these mutations in the CF population. In terms of the G and RF mutations recruited, 14 RFs were recruited, and 10Gs were recruited, these 24 mutations are considered to cover the vast majority (> 95%) of patients with G and RF mutations. However not all of these were treated with ELX/TEZ/IVA, only 12RFs, and 7Gs are represented at least once in the ELX/TEZ/IVA group. In order to provide a more complete assessment of the effect of ELX/TEZ/IVA across the various G and RF mutations, the MAH provided an analysis of available efficacy data for the patients treated with control in 104, who then moved to ELX/TEZ/IVA in the open-label study 110, to see if those genotypes derived a response.

Endpoints

For Study 104, the primary endpoint was absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group. The comparison for FEV1 to the control group (IVA and TEZ/IVA treatments) is made as a key secondary endpoint (step 3 in the confirmatory hierarchical testing procedure). The absolute changes from baseline in SwCL (both with and without comparison to the control group) are also included as key secondary endpoints. The other secondary and exploratory efficacy endpoints such as SwCL, CFQ-R score, and BMI are all accepted endpoints in CF clinical studies.

Importantly, the study sample size was chosen based on power calculations for the overall ELX/TEZ/IVA group. Therefore, the study was not powered for between-group comparisons nor designed for subgroup analyses (F/RF and F/G). An alternative design to enable a between group primary comparison for F/G (ELX/TEZ/IVA versus IVA) and a between group primary comparison for F/RF (ELX/TEZ/IVA versus TEZ/ IVA) would have been more informative from a regulatory perspective. However, if the control group does not change over time (i.e. the change in this group is around 0 on average), the study could have sufficient power to assess between-group difference. Even if the study isn't powered for this comparison, it could be seen that the control group behaves as expected in comparison with the ELX/TEZ/IVA group. However, as a change in the control group would bring the results into doubt, a formal between-group comparison is preferred and also included as secondary endpoint. It should however be noted that these analyses may be underpowered depending on the numbers in the subgroups as discussed further below in this section.

The same limitations as outlined above for the primary endpoints, also apply to the key secondary endpoints (FEV1 and SwCl).

The remaining secondary endpoints were not controlled for multiplicity: within group and between group absolute change in CFQ-R RD through week 8 from baseline, absolute change from baseline in CFQ-R RD through week 8 in treatment versus control, and absolute change from baseline in BMI at week 8 in treatment versus control.

Due to the COVID-19 pandemic, also home assessments of FEV1 and CFQ-R were permitted. Sensitivity analyses are included to verify the results based on clinic only or on the clinic and home assessments. Based on the unforeseen circumstances, such an approach was considered acceptable by CHMP.

Statistical Analyses

The primary analysis was performed using a mixed-effects model for repeated measures (MMRM) with the absolute change from baseline at Day 15, Week 4 and Week 8 as the dependent variable. The primary result obtained from the model was the estimated within-group treatment difference through

Week 8 (average of Week 4 and Week 8) for the ELX/TEZ/IVA group. Similar analysis approaches were used for the secondary longitudinal endpoints, including the between-group treatment difference for ppFEV1 and SwCL. These statistical analysis approaches are in line with the analyses used to support the approval of the initial MAA. The statistical methods are broadly acceptable subject to the comment below:

Some of the Vertex study personnel were unblinded, specifically the role of the Vertex IWRS manager and the Vertex Clinical Supply Chain. These roles required access to drug assignments within the IWRS system to package and deliver study drug, manage packaging batch records, conduct investigations (e.g., deviations or product complaints), and monitor sites' study drug inventories. It can be agreed that these particular roles can necessitate unblinding. To maintain the integrity of the trial, unblinded personnel had restrictions to ensure they did not share treatment assignments with blinded personnel.

The MMRM models used to analyse the primary and key secondary endpoints did not include comparator-by-treatment, comparator-by-visit and comparator-by-treatment-by-visit interaction terms as a fixed effects. Upon request by CHMP, the MAH provided results for the primary and key secondary endpoints, including these three terms in the MMRM model. The results of these sensitivity analyses were consistent with the primary analyses.

The MAH summarized the missing data patterns for the ppFEV1 and SwCl variables across Day 15, week 4 and week 8 visits by treatment and mutation class, i.e. (F/G ELX/TEZ/IVA; F/G IVA; F/RF ELX/TEZ/IVA; F/RF TEZ/IVA). The MAH has categorised missing data causes into two categories. The missing at random assumption is considered plausible for category 2 missing data (including missed visits due to COVID) while missing not at random is considered more plausible for category 1 missing data.

The MAH as requested presented sensitivity analyses for between-group comparisons of the absolute change in ppFEV1 from baseline through week 8 using a reference-based imputation approach for (a) the overall trial population and (b) each comparator subgroup. Reference-based imputation was performed separately by comparator group. The least-squares mean at each visit (Day 15, Week 4, Week 8) were provided.

Efficacy data and additional analyses

When viewing the baseline characteristics, it is noticed that the included populations might have a relative milder CF severity, than was included in the studies in the Symkevi and Kalydeco registration dossier (see **Table** 31). Especially the SwCl baseline values are lower in study 104 than pivotal studies submitted for the initial marketing authorisation. The baseline levels are measured after the 4-week TEZ/IVA or IVA run-in period. After these 4 weeks an effect of TEZ/IVA is indeed expected, which explains that these lower SwCL levels are comparable to SwCl values after IVA or TEZ/IVA treatment in the F/G and F/RF patients in registration studies for Kalydeco and Symkevi, respectively.

Table 31: Summary of baseline characteristics of study 104 and the registration studies for Symkevi and Kalydeco.

	All (n=258)	**F/RF (n=163)**	**F/G (n=95)**	**VX14-661-108 (n=244)** **(F/RF Symkevi)**	**VX12-770-111 (n=39)** **Non-G551D gating, Kalydeco)**	**VX08-770-102 (n=161)** **G551D gating, Kalydeco**	**VX11-770-110 (n=69)** **R117H, Kalydeco**

FEV1, mean (SD)	67.6 (16.0)	67.9 (16.3)	67.0 (15.6)	62.3 (14.5)	78.38 (20.98)	63.6 (16.43)	72.9 (19.16)
SwCl, mean (SD)	58.0 (26.3)	63.0 (27.6)	49.3 (21.3)	69.9 (26.1)	97.54 (18.58)	100.24 (10.28)	70.49 (21.65)
BMI, mean (SD)	24.06 (4.7)	24.49 (5.21)	23.33 (3.59)	24.22 (5.06)	22.13 (4.99)	21.8 (3.56)	23.76 (6.13)
CFQ-R, mean (SD)	76.9 (16.2)	77.4 (15.8)	76.1 (16.9)	68.1 (17.7)	NA	NA	NA

Furthermore, some patients are included with baseline FEV1 values below <40 and over 90. It is anticipated that the inclusion criterion pertaining to screening ppFEV1 was met in all enrolled subjects in Study 104, but the ppFEV1 decreased at their baseline study visit.

In terms of the included genotypes with a gating mutation (IVA comparator group) represented in the clinical study, across the 95 F/G subjects, 10 different gating mutations have been represented. These are the 10 different mutations that are included in the Kalydeco label in the EU. For the genotypes with a residual function mutation (TEZ/IVA comparator group), across the 163 subjects, 14 different mutations have been represented. The R347H genotype is only included in the US label, but only 1 patient with this mutation is included in the study. The S977F mutations are also included in the EU Symkevi label, but not included in the study. This is considered acceptable as this mutation is very rare (CFTR2 database only includes 13 patients with this genotype). The fact that distribution of the included mutations is unequal (e.g. over half of the IVA comparator group has the G551D mutation) is related to the prevalence of these mutations in the CF population.

The MAH states that these 24 mutations cover the vast majority (> 95%) of patients with G and RF mutations; and this is agreed. However not all of these were treated with ELX/TEZ/IVA, only 12RFs, and 7Gs are represented at least once in the ELX/TEZ/IVA group. As requested by CHMP, in order to provide a more complete assessment of the effect of ELX/TEZ/IVA across the various G and R mutations, the MAH provided an analysis of available efficacy data for the patients treated with control in 104, who then moved to ELX/TEZ/IVA in the open-label study 110 (see further below).

With regard to prior medication, it is considered of importance to know which percentage of the subjects received TEZ or TEZ/IVA prior to the study. This is of importance as in the Kaftrio registration procedure, the ppFEV1 measurements were influenced by whether the patients were Vertex CFTR modulator naïve or experienced. The data at that time suggested that the screening period of 4 weeks may not have been sufficient for CFTR-modulator naïve patients randomized to TEZ/IVA to derive the full benefit of this treatment by time of baseline ppFEV1 assessment. The MAH performed subgroup analysis to compare treatment effect on ppFEV1, SwCl and CFQ-R in patients who already have been on Vertex CFTR modulators at recruitment to those who were treatment naïve. In general, less F/RF patients were on prior modulator therapy compared to F/G patients. However, in the separate patient populations, the prior modulator use is balanced between placebo and active treatment group (see further below for efficacy results).

Efficacy results for the total population

For the primary endpoint, the absolute within-group change in ppFEV1 from baseline through week 8 of ELX/IVA/TEZ group was 3.7% (95% CI: 2.8, 4.6; p<0.0001). As FEV1 is linked to mortality, any significant difference is considered potentially clinically relevant. The result of the sensitivity analysis, a MMRM based on multiple imputations (MI), was consistent with the primary analysis. The FEV_1

absolute change in ppFEV1 compared to the control group was a key secondary endpoint. The result of this analysis was consistent with the within-group changes (3.5; 95% CI: 2.2, 4.7; p<0.0001).

Taken alone, and without considering the design and arising uncertainties regarding the interpretation, a gain of 3.7 ppFEV1 could be accepted as clinically relevant, while not overwhelming. However, given the diversity of the patients recruited (24 genotypes, both F/G and F/RF genotypes), some genotypes may not have gained a clinically significant amount of FEV_1 function. If the absolute within-group improvement had been more substantial, the possibility that there may be some genotypes not gaining benefit would be less of a concern. As will be later discussed in this section, this concern applies in particular to the F/RF group. A sensitivity analysis was performed using the multiple imputation method to assess for impact of missing data, and results were consistent with the primary analysis.

For the key secondary endpoint, the absolute within-group change in SwCl from baseline through week 8 of ELX/IVA/TEZ was -22.3 (95% CI: -24.5, -20.2; p<0.0001). This reduction is considered clinically relevant (MCID:-10 mmol/L). The SwCl comparison with the control group was consistent and resulted in a reduction of 23.1 mmol/L (95% CI: -26.1, -20.1; p<0.0001).

Other secondary endpoints included the change in CFQ-R RD score from baseline both within-group changes and compared to the control group. The additional endpoints are not under type I error control, and as such, can only be considered as supportive data. The within-group difference is an increase in score of 10.3 points (95% CI: 8.0, 12.7; nominal p<0.0001) and compared to the control group the treatment with ELX/TEZ/IVA resulted in an increase of 8.7 points (95% CI: 5.3, 12.1; nominal p<0.0001). A difference of over 4 points in CFQ-R RD score is considered to be clinically relevant. Other CFQ-R domains (Physical and Vitality) indicated an improvement with the triple combination compared to the comparator group.

Upon request by CHMP and in order to establish the proportion of the treatment group that achieved a meaningful gain in FEV1, SwCL and CFQ-R RD, a responder analysis was provided for the primary outcome using a threshold of 1.5% and 2.5% ppFEV1, and separately by comparator group. Substantial increases in the proportion of ppFEV1, SwCl and CFQ-R RD responders were observed with ELX/TEZ/IVA compared to the control arms. With ELX/TEZ/IVA, 49.6% of the patient benefited of over 2.5% in ppFEV1, compared to 22.8% in the control group. A very similar effect size was seen for SwCL and CFQ-R RD score.

For ppFEV1 and also for the CFQ-R additional analyses were performed, including spirometry data from a home-setting and CFQ-R data from only the clinic setting. These also showed consistent results with the main analyses for these endpoints.

Nevertheless, a downside of the current study design is that the effect in the separate F/G and F/RF population was not tested. Since these populations usually have a different CF severity and because the standard CFTR modulator is different in these population, it was considered important to see whether an additional benefit was seen when treated with ELX/TEZ/IVA over the approved therapy IVA or TEZ/IVA. Considering the hypothesis that the mechanism of action is mainly through the *F508del* allele, a beneficial effect over the approved therapies would have been expected. ELX/TEZ/IVA might also act via the non-F508del allele. Therefore, a difference in effect size might be present between subjects with a gating or a residual function mutation. Therefore, the MAH was requested to include also analyses of the primary and key secondary endpoints per genotype/comparator group (F/G and F/RF); those are discussed below

F/G population

In the F/G population, TEZ/IVA dual therapy (which mainly works on the non-F508del allele) did not result in a clinically relevant benefit. As ELX/TEZ/IVA is suggested to act trough the *F508del* allele, an effect over IVA is anticipated in this population. Within-group and between-group analyses for ppFEV1,

SwCL and CFQ-R RD in the F/G population were provided. Consistent with the within-group difference, the between-group data showed a beneficial change in ppFEV1 of 5.8 percentage point (95% CI: 3.5, 8.0; nominal p<0.0001), in SwCL of -20.0 mmol/L (95% CI: -25.4, -14.6; nominal p<0.0001) and in CFQ-R RD of 8.9 points (95% CI: 3.8, 14.0; nominal p=0.0008). These results are all considered clinically relevant, and indicated that the ELX/TEZ/IVA has a beneficial effect in the F/G population over IVA monotherapy. The gain in ppFEV1 seen in the F/G group was in line with the expectations based on the 'treat the F' treatment paradigm (effect on *F508De*l allele) put forward by the MAH. The cumulative effect of the 3 agents is very similar to what was achieved in F/MF CF patients.

F/RF population

Based on the MAHs *F508del* hypothesis, ELX/TEZ/IVA would be expected to generate a positive clinical outcome in the F/RF population. Consistent with the within-group difference, the between-group data showed a beneficial change in ppFEV1 of 2.0 percentage point (95% CI: 0.5, 3.4; nominal p=0.0093), in SwCL of -24.8 mmol/L (95% CI: -28.4, -21.2; nominal p<0.0001) and in CFQ-R RD of 8.5 points (95% CI: 4.0, 13.1; nominal p=0.0003). The magnitude of effects on SwCl and CFQ-R with ELX/TEZ/IVA were similar when compared to the F/G population. However, the ppFEV1 benefit was lower, with an increase of 2.0 percentage points compared to TEZ/IVA. This increase was lower than initially expected. Based on the response to ELX/TEZ/IVA seen in F/F and F/MF patients, and the 'treat the F theory' it would be anticipated that treating an F/RF patient with ELX/TEZ/IVA might bring a total gain in ppFEV1 of approximately 14%. A greater response with F/RF patients would have been anticipated with the triple combination compared to the reasonably modest ppFEV1 6.8% observed in Study VX14-661-108 with TEZ/IVA over placebo. It would have been expected that the F/RF patients should have gained more in ppFEV1 than the F/G patients, whereas in fact, the F/G patients seem to have gained a better response.

A similar pattern was noticed in the real-world US registry data, where F/G patients also seemed to get a better response to triple combination versus F/RF patients. While it is agreed that a gain of 2% over TEZ/IVA can be considered clinically relevant for patients with an F/RF genotype, some uncertainties remained on whether all F/RF patients will have achieved a clinically meaningful response.

The reason why F/RF subjects had lower ppFEV1 improvements on ELX/TEZ/IVA compared to F/MF, F/F, and F/G subjects was unclear, but it may be related to reduced severity of CF in F/RF patients. RF mutations, which are generally Class IV or Class V, cause a more modest reduction in CFTR function compared to Class I, II, and III mutations, such as MF mutations, the F508del mutation, and the G551D mutation, respectively. As a result, untreated patients with RF mutations have a less severe CF phenotype, characterized by later diagnosis, lower baseline SwCl, a lower prevalence of pancreatic insufficiency, and a slower pace of lung function decline compared to patients with Class I, II, and III mutations; however, they continue to have signs and symptoms of CF and premature mortality. These differences in RF patients' underlying disease progression and age at diagnosis may impact the potential for CFTR modulator treatment to increase ppFEV1.

Nevertheless, overall the totality of the data supported conclusions of an effect, with a 95% CI between 0.5 and 3.4 percentage points. Although, an MCID for FEV1 cannot be defined, according to the "EMA report of the workshop on endpoints for cystic fibrosis clinical trials" dated 2012, a treatment effect equivalent to the average annual loss in FEV1 can be considered as clinically relevant. Based on published literature, the annual rate of ppFEV1 decline in RF patients is around 0.70. When excluding R117H patients from the cohort, the annual decline is -1.05. Considering these annual decline rates, the 2.0 percentage point was ultimately considered clinically relevant. Furthermore, clinically relevant improvements in SwCL and CFQ-R further supported the efficacy of Kaftrio in F/RF CF patients.

To put the efficacy results in the F/RF population into perspective. In the initial Symkevi procedure (study VX14-661-108), TEZ/IVA showed improvements over placebo of ppFEV1 of 6.8 percentage

points, -9.5 mmol/L in SwCl and of 11.1 points in CFQ-R in the F/RF population. When compared to IVA monotherapy the benefit in ppFEV1 was 2.1 percentage points, and for CFQ-R it was 1.4 points increase.

In total, the efficacy outcomes for ELX/TEZ/IVA are considered to show a clinically relevant improvement over the approved control therapy IVA or TEZ/IVA in the F/G and F/RF population, respectively.

The applicant has provided requested data from subjects 65 years and older. Although the preliminary data from ongoing Study 110 are limited to 6 patients and the study was not powered for a subgroup analysis of subjects at least 65 years of age, the data provide an idea on the benefit in these older patients. Nevertheless, the numbers remain insufficient to determine whether responses in these patients is different from younger adults. The paragraphs on elderly patients already included in the SmPC section 5.2 remain appropriate.

Additional analyses performed by comparator group

As indicated above, the main interest lays in the effect in the two separate comparator groups. To evaluate the effects in the F/G and F/RF populations further and more in depth, some additional analysis were requested and performed by the MAH. Due to the COVID-19 pandemic, additional sensitivity analyses were done for pooled clinic and home assessment of the ppFEV1 and or clinic only CFQ-R scores. The MAH provided these analyses also for the subgroups by the comparator. Results were consistent with the original subgroup analysis per comparator subgroup.

The MAH has also performed subgroup analyses for age, sex, baseline lung function, and geographic region per comparator subgroup. In general, the results of these subgroup analyses were also consistent with the overall results per comparator group.

In addition, the MAH performed subgroup analysis to compare treatment effect on ppFEV1, SwCl and CFQ-R in patients who already have been on Vertex CFTR modulators at recruitment to those who were treatment naïve. In general, a beneficial effect is seen for all three parameters in both patients CFTR modulators experienced and CFTR modulator naïve. However, in the F/RF population the effects on ppFEV1 (1.7% vs 2.8%) and SwCL (-16.4 mmol/L vs -28.7 mmol/L) seem to be less pronounced in the patients who were already treated with an Vertex CFTR modulator compared to those who were treatment-naive. Although it is generally accepted that a run-in period of 4 weeks is sufficient to obtain an on-treatment baseline, these efficacy results suggest that a maximum effect might not be completely established after 4 weeks. This was also reflected in the results of the comparator groups. Therefore, the overall data in F/RF reflect mainly the results of the 2/3 of the patients who were not on prior Vertex CFTR modulator treatment before inclusion in Study 104. However, the limited number of patients hampers a firm interpretation of these results. Moreover, the efficacy outcomes for SwCL and CFQ-R RD score in both patients with and without prior CFTR modulator therapy are still highly clinically relevant. Therefore, these results do not further influence the B/R assessment. Also, per comparator subgroup, responder analyses were performed. Substantial increases in the proportion of ppFEV1, SwCl and CFQ-RD responders are observed for the TEZ comparator group. While more modest increases are observed for the TEZ/IVA comparator group, these could still be considered clinically relevant.

Data from follow-up study 110 suggest that patients treated with control in Study 104 and who then switched to Kaftrio in Study 110 had improvements in ppFEV1, SwCl, and CFQ-R that are very similar to those seen in Study 104 treatment group, in both the F/G and F/RF categories at week 8. While the preliminary data from ongoing Study 110 are limited and the study was not powered for these

subgroup analyses, the analyses are supportive of the results of Study 104. The data also suggest that the gains in the Kaftrio treated group of Study 104 were maintained in Study 110.

Updated registry data were presented for those patients with F/G and F/RF genotypes. ppFEV1 increased by an average of 4.3 percentage points in the F/G group and of 3.0 percentage points in the F/RF group. The RWE analysis further confirms the beneficial effects of ELX/TEZ/IVA seen in study 104.

To identify the robustness of the effect and see whether different gating and residual function mutation might influence the effect size, it is of interest to see the clinical benefit in a subset based on specific mutations. Genotype level data were provided for Study 104, Study 110 and for the updated registry data. For almost all of the genotypes included in both the F/G and F/RF categories, clinical benefit of some degree can be seen, and in most cases, can be considered meaningful.

Overall, the presented additional analyses can be considered to support the conclusions of Study 104 and suggest that patients with F/G or F/RF mutation types improved with Kaftrio over currently approved therapy.

In study 104 patients representing a total of 24 mutations (RF and G) were recruited, 12 F/RFs and 7 F/Gs were represented (with at least one patient) in the ELX/TEZ/IVA treatment group; the remaining 5 were treated with appropriate control. Information on additional mutations were also provided from study 110 and the real-world effectiveness registry data. For almost all of the genotypes included in both the F/G and F/RF categories, clinical benefit of some degree can be seen, and in most cases, it can be argued to be meaningful. Overall, the CHMP considered that the totality of the data provides sufficient information on patients with RF and G mutations but also to conclude that Kaftrio works in patient with at least one F508del mutation.

Indication

Overall, Kaftrio is currently approved for F/F and F/MF mutations and demonstration of efficacy has been demonstrated in F/RF and F/G patients as discussed in this application. The CHMP therefore agreed with the applicant, that hypothesis of efficacy based at least an F508del mutation on one allele is demonstrated and considered the broad indication approvable:

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

2.4.3. Conclusions on the clinical efficacy

The efficacy outcomes for ELX/TEZ/IVA in study 104 are considered to show a clinically relevant improvement in ppFEV1, SwCL, and CFQ-R RD score over the approved control therapy IVA or TEZ/IVA in the F/G and F/RF populations, respectively.

Based on these results, the added benefit of the triple combination over approved therapies can be determined, and its plausibility that the ELX/TEZ/IVA is mainly acting through the *F508del* allele is considered now demonstrated.

The effects of ELX/TEZ/IVA in the F/MF (study 102), F/F (study 103), F/RF (study 104) and F/G (study 104) population and the maintained effects as seen in study 105 are sufficient to conclude on the benefit of ELX/TEZ/IVA in the entire CF population of patients aged 12 years and older with at least one F508del allele.

2.5. Clinical safety

Introduction

The safety profile of ELX/TEZ/IVA was characterized based on a comprehensive review of data from the clinical development program described in the initial ELX/TEZ/IVA MAA, which included over 700 subjects who had received at least 1 dose of ELX as monotherapy or as part of a triple combination regimen.

The safety profile was mainly based on the pivotal study in patients with F/MF mutations. Long-term safety data were evaluated in the ongoing open-label extension Study 105, which included 271 subjects with ≥48 weeks of cumulative ELX/TEZ/IVA exposure (through IA2).

Overall, ELX/TEZ/IVA was generally safe and well-tolerated. Adverse drug reactions (ADRs) were generally mild or moderate in severity. Important AEs observed with incidence rates ≥ 3% and ≥1% more frequent than placebo are influenza, wheezing and hypoglycaemia.

In Study 102, Grade 3-4 AEs were reported for 9.4% (ELX/TEZ/IVA) vs. 7.5% (placebo) of patients. Grade 3 or 4 AEs with an incidence of at least 1% in either treatment group were infective pulmonary exacerbation of cystic fibrosis (4.5%, placebo), blood creatine increased (2.0%, ELX/TEZ/IVA), ALT increased (1%, ELX/TEZ/IVA), and AST increased (1%, ELX/TEZ/IVA).

SAEs were reported for 13.9% in the ELX/TEZ/IVA group and 20.9 % in the placebo group. The SAEs that occurred in ≥1% of patients in either treatment group were infective PEx of CF (5.4% vs. 16.4%), haemoptysis (1.0% vs. 1.5%) and rash (1.0% vs. 0.5%) and influenza (1.5% vs 0%). Related SAEs occurred in 3.0% (ELX/TEZ/IVA) vs. 1.0% (placebo). No related SAEs occurred in 2 or more patients in either treatment group.

Rash occurred more frequently in the ELX/TEZ/IVA group (10.9%, 22 subjects) than in the placebo group (6.5%, 13 subjects).

AEs of CK elevation occurred more frequently in subjects in the ELX/TEZ/IVA group compared to the placebo group. The majority were asymptomatic laboratory elevations, many of which were preceded by exercise. The two subjects in the ELX/TEZ/IVA group presented with AEs of rhabdomyolysis with CK elevations did not have clinical features of rhabdomyolysis.

Discontinuations due to AEs occurred were low.

The long-term safety data (Study 105 Safety Set, OLS) showed decreased exposure-adjusted event rate of (related AEs), Grade 3-4 AEs, SAEs with ELX/TEZ/IVA compared to the Study 102 Safety Set. In the Cumulative Safety Set, the safety profile is quite similar to the safety profile of Study 102 Safety Set.

The Study 104 Safety Set in CF patients with F/G and F/RF mutations includes all subjects who received at least 1 dose of study drug in the Study 104 Treatment Period (i.e., does not include subjects who were only dosed in the IVA or TEZ/IVA Run-in Period).

Patient exposure

A total of 258 subjects received at least 1 dose of study drug in the Treatment Period. The exposure was similar between treatment groups. The mean exposure was 8.0 (0.7) weeks for the 132 subjects in ELX/TEZ/IVA group and 7.9 (0.9) weeks for the 126 subjects in the control group (Table 32).

Table 32 Summary of Exposure Safety Set for the Treatment Period

	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
Total exposure (patient weeks)	993.4	1050.4	2043.9
Exposure duration (weeks)			
n	126	132	258
Mean (SD)	7.9 (0.9)	8.0 (0.7)	7.9 (0.8)
Median	8.0	8.0	8.0
Min, max	1.3, 9.1	0.6, 9.0	0.6, 9.1
Exposure duration by interval, n (%)			
≤2 weeks	2 (1.6)	1 (0.8)	3 (1.2)
>2 - ≤4 weeks	1 (0.8)	0	1 (0.4)
>4 - ≤8 weeks	77 (61.1)	82 (62.1)	159 (61.6)
>8 weeks	46 (36.5)	49 (37.1)	95 (36.8)

The Study 104 Safety Set and Full analysis Set were identical.

Adverse events

In the Treatment Period, 88 (66.7%) subjects in the ELX/TEZ/IVA group and 83 (65.9%) subjects in the control group had at least 1 AE.

Table 33 presents an overview of AEs.
Five (3.8%) subjects in the ELX/TEZ/IVA group and 11 (8.7%) subjects in the control group had a serious AE (SAE). Five (3.8%) subjects in the ELX/TEZ/IVA group and 4 (3.2%) subjects in the control group had severe AEs; all other subjects with AEs had AEs that were mild or moderate in severity. One (0.8%) subject in the ELX/TEZ/IVA group and 2 (1.6%) subjects in the control group had AEs that led to study drug discontinuation. Five (3.8%) subjects in the ELX/TEZ/IVA group and 3 (2.4%) subjects in the control group had AEs that led to study drug interruption.

Table 33 Summary of AEs - Treatment Period (Safety Set)

Category, n (%)	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
Number of AEs (Total)	284	232	516
Subjects with any AEs	83 (65.9)	88 (66.7)	171 (66.3)
Subjects with AEs by strongest relationship			
Not related	45 (35.7)	35 (26.5)	80 (31.0)
Unlikely related	16 (12.7)	21 (15.9)	37 (14.3)
Possibly related	22 (17.5)	30 (22.7)	52 (20.2)
Related	0	2 (1.5)	2 (0.8)
Subjects with AEs by maximum severity			
Mild	50 (39.7)	58 (43.9)	108 (41.9)
Moderate	29 (23.0)	25 (18.9)	54 (20.9)
Severe	4 (3.2)	5 (3.8)	9 (3.5)
Life-threatening	0	0	0
Missing	0	0	0
Subjects with AEs leading to study drug discontinuation	2 (1.6)	1 (0.8)	3 (1.2)
Subjects with AEs leading to study drug interruption	3 (2.4)	5 (3.8)	8 (3.1)
Subjects with Grade 3/4 AEs	4 (3.2)	5 (3.8)	9 (3.5)
Subjects with related AEs[a]	22 (17.5)	32 (24.2)	54 (20.9)
Subjects with SAEs	11 (8.7)	5 (3.8)	16 (6.2)
Subjects with related SAEs[a]	2 (1.6)	0	2 (0.8)
Subjects with AEs leading to death	0	0	0

Source: Study 104 CSR/Table 14.3.1.1.2

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 version 23.0. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and 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 (serious) AEs, AEs with relationship of related, possibly related, and missing were counted.

In general, the safety pattern in the ELX/TEZ/IVA group is quite similar to the safety in the control group. A majority of all AEs were mild to moderate. There were no deaths arising from treatment in either group. Small differences were observed for grade 3/4 AEs and related AEs (more subjects in the ELX/TEZ/IVA group) and (related) SAEs (more subjects in the control group).

Treatment-emergent AEs

Table 34 presents common AEs that occurred in ≥5% of subjects in either treatment group.

Overall, the common AEs were mostly consistent with common manifestations or complications of CF disease in CF subjects 12 years of age and older or the known safety profile of ELX/TEZ/IVA.

The majority of the common AEs had a lower incidence in the ELX/TEZ/IVA group than in the control group. AEs with a higher incidence in the ELX/TEZ/IVA group (alanine transaminase [ALT] increased, aspartate transaminase [AST] increased, and abdominal pain) are all known adverse drug reactions for

ELX/TEZ/IVA treatment observed in previous studies. The same 8 subjects had AEs of ALT increased and AEs of AST increased.

Table 34 AEs Occurring in ⩾5% of Subjects in a Treatment Group by PT - Treatment Period (Safety Set)

Preferred Term, n (%)	Control N = 126	ELX/TEZ/IVA N = 132
Subjects with any AEs	83 (65.9)	88 (66.7)
Headache	19 (15.1)	11 (8.3)
ALT increased	0	8 (6.1)
AST increased	0	8 (6.1)
Abdominal pain	2 (1.6)	7 (5.3)
Sputum increased	8 (6.3)	6 (4.5)
Diarrhoea	8 (6.3)	5 (3.8)
Cough	18 (14.3)	3 (2.3)
Infective PEx of CF	13 (10.3)	3 (2.3)
Nausea	9 (7.1)	2 (1.5)

Source: Study 104 CSR/Table 14.3.1.3

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; 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 23.0. 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.

Headache was the most frequent AE in both groups. After headache, in subjects in the ELX/TEZ/IVA group, the most frequent AEs were ALT and/or AST increased and abdominal pain, while in subjects in the control group, these were sputum increased, diarrhoea, nausea, cough, and infective PEx. Transaminase raises were previously shown to be more common with ELX/TEZ/IVA than with TEZ/IVA. This pattern has also been observed in the marketing authorisation. However, the numbers of events are much lower, which can be attributed to the much shorter exposure to study treatment.

AEs by Relationship

The majority of AEs were assessed by the investigator as not related or unlikely related to study drug. Thirty (22.7%) subjects in the ELX/TEZ/IVA group and 22 (17.5%) subjects in the control group had an AE assessed as possibly related. Two (1.5%) subjects in the ELX/TEZ/IVA group and no subjects in the control group had an AE assessed as related.

Table 35 Related TEAEs Occurring in ≥2% of Subjects in a Treatment Group by System Organ Class and Preferred Term Safety Set for the Treatment Period

System Organ Class Preferred Term	Control N = 126 n (%)	ELX/TEZ/IVA N = 132 n (%)
Subjects with any related TEAEs	22 (17.5)	32 (24.2)
Investigations	2 (1.6)	10 (7.6)
Alanine aminotransferase increased	0	5 (3.8)
Aspartate aminotransferase increased	0	5 (3.8)
Gastrointestinal disorders	7 (5.6)	9 (6.8)
Diarrhoea	3 (2.4)	4 (3.0)
Nausea	3 (2.4)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	10 (7.9)	7 (5.3)
Sputum increased	4 (3.2)	2 (1.5)
Cough	5 (4.0)	0
Wheezing	3 (2.4)	0
Skin and subcutaneous tissue disorders	3 (2.4)	5 (3.8)
Eye disorders	0	4 (3.0)
Nervous system disorders	7 (5.6)	4 (3.0)
Headache	6 (4.8)	4 (3.0)

AEs by Severity

The majority of subjects overall had AEs that were mild (41.9%) or moderate (20.9%) in severity; there were no life-threatening AEs. Five (3.8%) subjects in the ELX/TEZ/IVA group and 4 (3.2%) subjects in the control group had severe AEs. Severe AEs of infective pulmonary exacerbation (PEx) of CF occurred in 2 (1.5%) subjects in the ELX/TEZ/IVA group and 2 (1.6%) subjects in the control group. All other severe AEs occurred in one subject. Table 36).

Table 36 Grade 3/4 TEAEs by System Organ Class and Preferred Term Safety Set for the Treatment Period

System Organ Class Preferred Term	Control N = 126 n (%)	ELX/TEZ/IVA N = 132 n (%)
Subjects with any Grade 3/4 TEAEs	4 (3.2)	5 (3.8)
Infections and Infestations	2 (1.6)	2 (1.5)
Infective pulmonary exacerbation of cystic fibrosis	2 (1.6)	2 (1.5)
Cellulitis	0	1 (0.8)
Hepatobiliary disorders	0	1 (0.8)
Cholecystitis	0	1 (0.8)
Investigations	0	1 (0.8)
Alanine aminotransferase increased	0	1 (0.8)
Aspartate aminotransferase increased	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0	1 (0.8)
Haemoptysis	0	1 (0.8)
Gastrointestinal disorders	1 (0.8)	0
Gastritis	1 (0.8)	0
Psychiatric disorders	1 (0.8)	0
Anxiety	1 (0.8)	0
Depression	1 (0.8)	

- MedDRA version 23.0.
- A subject with multiple events within a category is counted only once in that category.
- Table is sorted in descending order of frequency of the ELX/TEZ/IVA column by System Organ Class, and by Preferred Term within each System Organ Class.

Adverse Events of Special Interest

AESIs were defined as AEs related to elevated transaminases and AEs related to rash.

Elevated Transaminase Events

Eight (6.1%) subjects in the ELX/TEZ/IVA group and 1 (0.8%) subject in the control group had at least 1 elevated transaminase event, none of which were serious. Of the 8 subjects who had AEs of transaminase elevations in the ELX/TEZ/IVA group, 5 had modest ALT or AST elevations (<3 × ULN), and 2 had ALT or AST elevations >3 to ≤5 × ULN. The remaining 1 subject had ALT >8 × ULN, and AST >5 × ULN and discontinued study drug and the study. No subjects in the control group discontinued study drug due to AEs of transaminase elevations. No subjects in the ELX/TEZ/IVA group and 1 (0.8%) subject in the control group interrupted study drug due to AEs of transaminase elevations. No subjects had transaminase elevations with concurrent total bilirubin elevations.

In the ELX/TEZ/IVA group, elevated transaminase events had a mean (SD) duration of 19.4 (7.8) days and mean (SD) time-to-onset of 18.3 (19.6) days. The 1 elevated transaminase event in the control group had a duration of 16.0 days and time-to-onset of 1.0 day.

Table 37 Summary of AESI: Treatment-emergent Elevated Transaminase Events Safety Set for the Treatment Period

	Control N = 126	ELX/TEZ/IVA N = 132
Subjects with any events, n (%)	1 (0.8)	8 (6.1)
Alanine aminotransferase abnormal	0	0
Alanine aminotransferase increased	0	8 (6.1)
Aspartate aminotransferase abnormal	0	0
Aspartate aminotransferase increased	0	8 (6.1)
Hepatic enzyme abnormal	0	0
Hepatic enzyme increased	0	0
Hypertransaminasaemia	0	0
Liver function test abnormal	0	0
Liver function test increased	1 (0.8)	0
Transaminases abnormal	0	0
Transaminases increased	0	0
Subjects with any events by maximum severity, n (%)		
Mild	1 (0.8)	5 (3.8)
Moderate	0	2 (1.5)
Severe	0	1 (0.8)
Life-threatening	0	0
Missing	0	0
Subjects with events leading to treatment discontinuation, n (%)	0	1 (0.8)
Subjects with events leading to treatment interruption, n (%)	1 (0.8)	0
Subjects with serious events, n (%)	0	0
Subjects with related serious events, n (%)	0	0
Subjects with events leading to death, n (%)	0	0
Duration of events (days)		
Number of events	1	17
Number of events with non-missing duration	1	11
Mean (SD)	16.0 (--)	19.4 (7.8)
Median	16.0	19.0
Min, max	16, 16	4, 29
Time-to-onset of first event (days)		
Subjects with event with complete start date	1	8
Mean (SD)	1.0 (--)	18.3 (19.6)
Median	1.0	13.5
Min, max	1, 1	1, 57

- Elevated transaminase events were coded using MedDRA version 23.0.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing are counted.
- 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.
- Preferred Terms are sorted by alphabetical order.

Rash Events

Four (3.0%) subjects in the ELX/TEZ/IVA group and 5 (4.0%) subjects in the control group had at least 1 rash event. All rash events were mild or moderate in severity. No rash event was serious or led to study drug discontinuation. Rash events resulted in study drug interruption for 1 (0.8%) subject in the ELX/TEZ/IVA group and 1 (0.8%) subject in the control group.

In the ELX/TEZ/IVA group, 1 subject with rash events was male and 3 subjects were female, none of whom were taking hormonal therapy. In the control group, 2 subjects with rash events were male and 3 subjects were female, 2 of whom were taking hormonal therapy.

In the ELX/TEZ/IVA group, the mean (SD) duration of rash events was 6.0 (3.2) days and the mean (SD) time-to-onset was 25.8 (14.0) days. In the control group, the mean (SD) duration of rash events was 16.4 (19.7) days and mean (SD) time-to-onset was 18.0 (17.0) days.

Influenza

Influenza is listed as a common AE in the SmPC for ELX/TEZ/IVA and is also listed in Section 4.8 for IVA. In Study 104 there were only 4 cases of influenza listed as an AE in total, 2 each for both the treatment (1.5%) and control (1.6%) groups. Influenza appears to have been less frequent in Study 104 and there was no increase seen in the treatment group vs control.

Serious adverse event/deaths/other significant events

There were no deaths reported.

Other SAEs

SAEs were more common in the control group than in the ELX/TEZ/IVA group. Five (3.8%) subjects in the ELX/TEZ/IVA group and 11 (8.7%) subjects in the control group had at least 1 SAE.

SAEs of infective PEx occurred in 2 (1.5%) subjects in the ELX/TEZ/IVA group and 7 (5.6%) subjects in the control group; all other SAEs occurred in no more than 1 subject per treatment group.

Table 38 Serious AEs by PT–Treatment Period (Safety Set)

Preferred Term, n (%)	Control N = 126	ELX/TEZ/IVA N = 132
Subjects with any serious AEs	11 (8.7)	5 (3.8)
Infective PEx of CF	7 (5.6)	2 (1.5)
Cellulitis	0	1 (0.8)
Tinnitus	0	1 (0.8)
Cholecystitis	0	1 (0.8)
Haemoptysis	1 (0.8)	1 (0.8)
Pneumonia	1 (0.8)	0
Hyperparathyroidism primary	1 (0.8)	0
Anxiety	1 (0.8)	0
Depression	1 (0.8)	0

Source: Table 14.3.2.2

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 23.0. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency of the ELX/TEZ/IVA column by PT.

The majority of SAEs were assessed by the investigator as unlikely related or not related to study drug. Two (1.5%) subjects in the ELX/TEZ/IVA group and no subjects in the control group had an AE assessed as related.

Table 39 Related Serious TEAEs by System Organ Class and Preferred Term Safety Set for the Treatment Period

System Organ Class Preferred Term	Control N = 126 n (%)	ELX/TEZ/IVA N = 132 n (%)
Subjects with any related serious TEAEs	2 (1.6)	0
Psychiatric disorders	1 (0.8)	0
Anxiety	1 (0.8)	0
Depression	1 (0.8)	0
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0
Haemoptysis	1 (0.8)	0

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

Laboratory findings

Haematology

There were no clinically relevant trends in haematology parameters in the ELX/TEZ/IVA group or the control group.

Overall, AEs related to haematology were infrequent (no PT occurred in more than 1 subject (Table 40). None of the AEs related to haematology was serious or led to treatment discontinuation or interruption.

Non-LFT chemistry

There were no clinically relevant trends in mean values of other non-LFT chemistry parameters.

Overall, AEs related to non-LFT chemistry parameters were infrequent (no PT occurred in more than 2 subjects in a treatment group) and had a similar overall incidence between treatment groups (Table 40).

None of these AEs was serious or led to treatment discontinuation or interruption.

Table 40 TEAEs for System Organ Class Investigations by Preferred Term: Treatment Period Safety Set for the Treatment Period

System Organ Class Preferred Term	Control N = 126 n (%)	ELX/TEZ/IVA N = 132 n (%)
Investigations	7 (5.6)	15 (11.4)
Alanine aminotransferase increased	0	8 (6.1)
Aspartate aminotransferase increased	0	8 (6.1)
Blood bilirubin increased	0	4 (3.0)
Gamma-glutamyltransferase increased	0	3 (2.3)
Bilirubin conjugated increased	0	2 (1.5)
Blood creatine phosphokinase increased	0	2 (1.5)
Amylase increased	0	1 (0.8)
Blood urea increased	0	1 (0.8)
C-reactive protein increased	0	1 (0.8)
Glucose tolerance test abnormal	0	1 (0.8)
Platelet count increased	0	1 (0.8)
Reticulocyte count increased	0	1 (0.8)
White blood cells urine positive	0	1 (0.8)
Bacterial test positive	2 (1.6)	0
Body temperature fluctuation	1 (0.8)	0
Crystal urine present	1 (0.8)	0
Lipase increased	1 (0.8)	0
Liver function test increased	1 (0.8)	0
Pulmonary function test decreased	1 (0.8)	0
Weight decreased	2 (1.6)	0

- MedDRA version 23.0.
- A subject with multiple events within a category is counted only once in that category.

LFT

Mean concentrations of LFT parameters were variable over time, but remained within normal range in both groups.

In the ELX/TEZ/IVA group, ALT or AST >3, >5, and >8 × ULN occurred in 4 (3.2%), 1 (0.8%), and 1 (0.8%) subject(s), respectively (Table 41). In the control group, ALT or AST >3, >5, and >8 × ULN occurred in 2 (1.6%), 1 (0.8%), and 0 subject(s), respectively. There were no subjects with ALT or AST >3 × ULN with total bilirubin >2 × ULN in either group.

Table 41 Threshold Analysis of LFT Chemistry Parameters - Treatment Period (Safety Set)

Parameter Subjects With Non-missing Post-baseline Data Post-baseline Threshold Analysis Criteria, n (%)	Control N = 126	ELX/TEZ/IVA N = 132
ALT (U/L) or AST (U/L)		
Total, N1	123	125
(ALT >ULN to ≤3 × ULN) or (AST >ULN to ≤3 × ULN)	13 (10.6)	30 (24.0)
(ALT >3 to ≤5 × ULN) or (AST >3 to ≤5 × ULN)	1 (0.8)	3 (2.4)
(ALT >5 to ≤8 × ULN) or (AST >5 to ≤8 × ULN)	1 (0.8)	0
(ALT >8 to ≤20 × ULN) or (AST >8 to ≤20 × ULN)	0	1 (0.8)
ALT >20 × ULN or AST >20 × ULN	0	0
(ALT >3 × ULN) or (AST >3 × ULN)	2 (1.6)	4 (3.2)
(ALT >5 × ULN) or (AST >5 × ULN)	1 (0.8)	1 (0.8)
(ALT >8 × ULN) or (AST >8 × ULN)	0	1 (0.8)
(ALT or AST) and total bilirubin		
Total, N1	123	125
(ALT >3 × ULN or AST >3 × ULN) and total bilirubin >2 × ULN	0	0

Source: Table 14.3.4.2

ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; GGT: gamma-glutamyl transferase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; TE: treatment-emergent; TEZ: tezacaftor; ULN: upper limit of normal

Notes: N1: the number of subjects with at least 1 non-missing measurement during the TE Period; n was the number of subjects in the post-baseline category. 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.

Bilirubin

In the ELX/TEZ/IVA group, increases from baseline in mean (SD) total bilirubin were observed, with a maximum increase of 3.8 (6.5) µmol/L at Week 4. The maximum increase in direct bilirubin in the ELX/TEZ/IVA group was 1.1 (1.5) µmol/L at both Week 4 and Week 8. There were no clinically relevant trends in total bilirubin or direct bilirubin in the control group.

The majority of subjects had bilirubin values that remained within the normal range. In the ELX/TEZ/IVA group, total bilirubin >2 and >3 × ULN occurred in 6 (4.8%) subjects and 2 (1.6%) subjects, respectively. In the control group, 1 (0.8%) subject had total bilirubin >2 × ULN and no subjects had total bilirubin >3 × ULN.

Vital Signs

Modest increases in blood pressure (BP) were observed. Overall, the findings were consistent with the results of previous ELX/TEZ/IVA studies described in the initial ELX/TEZ/IVA MAA.

At baseline, the ELX/TEZ/IVA group had a mean (SD) systolic blood pressure (SBP) of 118.5 (13.8) mmHg and diastolic blood pressure (DBP) of 72.1 (9.5) mmHg). The control group's baseline mean (SD) SBP was 117.4 (15.4) mmHg and DBP was 72.2 (9.7) mmHg. SBP and DBP increased during the treatment period in the ELX/TEZ/IVA group. The largest mean (SD) increase in SBP from baseline was 3.0 (12.4) mmHg (at Week 8) and the largest mean (SD) increase in DBP was 2.5 (8.9) mmHg (at Week 8). There were no clinically relevant trends in SBP or DBP in the control group.

SBP >140 mmHg occurred in 16 (13.0%) subjects in the ELX/TEZ/IVA group and in 12 (9.9%) subjects in the control group. DBP >90 mmHg occurred in 16 (13.0%) subjects in the ELX/TEZ/IVA group and 6 (5.0%) subjects in the control group.

There were no AEs of hypertension in either treatment group. One (0.8%) subject in the control group had an AE of hypotension.

There were no clinically relevant trends in temperature, respiratory rate, pulse rate, or pulse oximetry.

Safety in special populations

Adolescents

A total of 9 adolescents were enrolled in the control group and 15 adolescents in the ELX/TEZ/IVA group.

Of the subjects <18 years of age at screening, 6 (40.0%) subjects in the ELX/TEZ/IVA group and 5 (55.6%) subjects in the control group had at least 1 AE in the Treatment Period.

No subjects in the ELX/TEZ/IVA group had serious AEs (SAEs), severe AEs, or AEs that led to study drug discontinuation. One (11.1%) subject in the control group had severe SAEs in the SOC of psychiatric disorders that led to study drug discontinuation. No subjects in either treatment group had AEs that led to study drug interruption.

Most AEs in subjects <18 years of age at screening occurred in no more than 1 subject per treatment group by Preferred Term. AEs of headache and abdominal pain occurred in 2 (13.3%) subjects in the ELX/TEZ/IVA group and 3 (33.3%) subjects in the control group. Overall, the AEs were mostly consistent with common manifestations or complications of CF disease in CF subjects ≥12 to <18 years of age or with the known safety profile of ELX/TEZ/IVA.

Safety related to drug-drug interactions and other interactions

The safety related to drug-drug interactions and other interactions remains unchanged.

Discontinuation due to adverse events

One (0.8%) subject in the ELX/TEZ/IVA group and 2 (1.6%) subjects in the control group had AEs that led to study drug discontinuation (Table 42). In the ELX/TEZ/IVA group, 1 subject discontinued due to severe AEs of ALT increased and AST increased, which were not serious and assessed as possibly related to study drug. In the control group, 1 subject discontinued IVA treatment due to a moderate SAE of infective PEx of CF, which was assessed as not related to study drug, and 1 subject discontinued IVA treatment due to SAEs in the SOC of psychiatric disorders, which were assessed as possibly related to study drug.

Table 42 AEs Leading to Treatment Discontinuation by PT -Treatment Period (Safety Set)

Preferred Term, n (%)	Control N = 126	ELX/TEZ/IVA N = 132
Subjects with AEs leading to treatment discontinuation	2 (1.6)	1 (0.8)
ALT increased	0	1 (0.8)
AST increased	0	1 (0.8)
Infective PEx of CF	1 (0.8)	0
Anxiety	1 (0.8)	0
Depression	1 (0.8)	0

Source: Table 14.3.2.4
AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; 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 23.0. 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.

Adverse Events That Led to Interruption of Study Drug

Five (3.8%) subjects in the ELX/TEZ/IVA group and 3 (2.4%) subjects in the control group had AEs that led to study drug interruption. All of the subjects resumed study drug, except for 1 subject whose interruption occurred in Week 8 (Day 58). All AEs that led to study drug interruption occurred in 1 subject each. In the ELX/TEZ/IVA group, AEs that led to study drug interruption included pruritus, rash macular, tinnitus, tongue ulceration, bilirubin conjugated increased, blood bilirubin increased, and C-reactive protein increased. In the control group, AEs that led to study drug interruption included urticaria, gastritis, and LFT increased.

Post marketing experience

ELX/TEZ/IVA (Trikafta) was approved on 21 October 2019 (International Birth Date) in the US. ELX/TEZ/IVA (Kaftrio) was approved in the EU on 21 August 2020. Over 17,000 patients have been treated with commercial ELX/TEZ/IVA, representing more than 5,800 patient-years.

2.5.1. Discussion on clinical safety

General overview

The Study 104 Safety Set included 258 subjects, of which 132 subjects in ELX/TEZ/IVA group 126 subjects in the control group.

There were 88 (66.7%) subjects in the ELX/TEZ/IVA group and 83 (65.9%) subjects in the control group with at least one AE. Five (3.8%) subjects in the ELX/TEZ/IVA group and 4 (3.2%) subjects in the control group had severe AEs.

The most common AEs (occurring in ≥5% of subjects) in the ELX/TEZ/IVA group were headache, ALT increased, AST increased, and abdominal pain. The most common AEs (occurring in ≥5% of subjects) in the control group were headache, cough, infective PEx of CF, nausea, sputum increased, and diarrhoea.

Five (3.8%) subjects in the ELX/TEZ/IVA group and 11 (8.7%) subjects in the control group had SAEs. The majority of AEs were mild or moderate in severity. Infective PEx of CF occurred in 2 (1.5%)

subjects in the ELX/TEZ/IVA group and 7 (5.6%) subjects in the control group; all other SAEs occurred in no more than one subject per treatment group. There were no life-threatening AEs and no deaths.

One (0.8%) subject in the ELX/TEZ/IVA group had AEs that led to study drug discontinuation (ALT increased and AST increased), and 2 (1.6%) subjects in the control group had AEs that led to study drug discontinuation (1 subject with an SAE of infective PEx of CF and 1 subject with SAEs in the SOC of psychiatric disorders). Five (3.8%) subjects in the ELX/TEZ/IVA group and 3 (2.4%) subjects in the control group had AEs that led to treatment interruption.

Rash events (AESI of rash) occurred in 4 (3.0%) subjects in the ELX/TEZ/IVA group and 5 (4.0%) subjects in the control group. In the ELX/TEZ/IVA group, one subject with rash event was male, and 3 subjects with rash events were female, none of whom were taking hormonal therapy. All rash events in the ELX/TEZ/IVA group were mild or moderate in severity.

Eight (6.1%) subjects in the ELX/TEZ/IVA group and 1 (0.8%) subject in the control group had an AESI of elevated transaminases; the majority of events were mild or moderate in severity, and none were SAEs. One (0.8%) subject discontinued ELX/TEZ/IVA treatment due to AEs of ALT increased and AST increased.
In the ELX/TEZ/IVA group, ALT or AST >3, >5, and >8 × ULN occurred in 4 (3.2%), 1 (0.8%), and 1 (0.8%) subject(s), respectively. In the control group, ALT or AST >3, >5, and >8 × ULN occurred in 2 (1.6%), 1 (0.8%), and 0 subject(s), respectively. No subject had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN.

Two (1.5%) subjects in the ELX/TEZ/IVA group had AEs of blood creatine phosphokinase increased. Neither AE was serious or resulted in ELX/TEZ/IVA treatment discontinuation or interruption. No subject in the control group had an AE of blood creatine phosphokinase increased.

Mean SBP and DBP increased in the ELX/TEZ/IVA group. The largest mean (SD) increase in SBP from baseline was 3.0 (12.4) mm Hg (at Week 8) and the largest mean (SD) increase in DBP was 2.5 (8.9) mm Hg (at Week 8). No subjects had AEs related to increased blood pressure.

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

In Study 104, there was a higher frequency of transaminase elevations in the threshold analysis. Elevated transaminases are a known AE of ELX/TEZ/IVA. There are no new insights in this AESI. They are already addressed in the SmPC and RMP. No changes are proposed. Overall, the safety results appeared generally consistent with the known safety profile; no new safety concerns were identified on the provided data.

Study 104 is unusual in that both F/G and F/RF genotypes were combined and randomised as one group. No comparison of safety between F/G and F/RF genotypes has been provided. However, there is an overall low incidence of severe AEs, SAEs, AEs leading to low discontinuation/interruption across both the combined treatment group and combined control group, and no life-threatening AEs or AEs leading to death in either group. The safety data and AE profile from the combined F/G and F/RF group are also consistent with those in both F/F and F/MF genotype groups, and it is not anticipated that there would be a difference in safety in F/G v F/RF genotypes. For these reasons the value of a subgroup analysis by genotype group (F/G and F/RF) for safety is considered limited in terms of characterising safety in F/G v F/RFs.

The applicant has provided requested data from subjects 65 years and older. Although the preliminary data from ongoing Study 110 are limited to 6 patients, the data provide an idea on the benefit in these older patients. Nevertheless, the numbers remain insufficient to determine whether responses in these patients is different from younger adults. The paragraphs on elderly patients already included in the

SmPC section 5.2 remain appropriate.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

A total of 9 adolescents were enrolled in the control group and 15 adolescents in the ELX/TEZ/IVA group. The safety was generally consistent with the overall study population.

2.5.2. Conclusions on clinical safety

ELX/TEZ/IVA was generally safe and well-tolerated for 8 weeks.

Overall, the safety seen in Study 104 were consistent with either the common manifestations or complications of CF disease or with the known safety profile of ELX/TEZ/IVA. No new safety concerns were identified, but the number of subjects in the new safety set is relatively small and limited in terms of duration of follow up. However, the MAH agreed to include patients with F/G and F/RF mutations in the planned PASS category 3 study to gather additional long term safety data post approval.

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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

No changes to the list of safety concerns were introduced.

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

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
Not applicable				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
Not applicable				
Category 3 – Required additional PV activities (by the competent authority)				
Study in patients with moderate hepatic impairment (Study 007) Ongoing	Evaluate the safety, tolerability, and PK of ELX/TEZ/IVA in subjects without CF who have moderate hepatic impairment and in matched healthy subjects	• Use in patients with moderate hepatic impairment	Final Report	Q3 2020
Open-label extension study (Study 105) Ongoing	Evaluate the long-term safety, tolerability, and efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in subjects 12 years of age and older with CF, homozygous or heterozygous for the *F508del-CFTR* mutation	• Susceptibility for influenza virus infections • Hepatotoxicity • Cataract • Long-term safety	Final Report	31 December 2022
PASS Planned	Evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting	• Susceptibility for influenza virus infections • Hepatotoxicity • Use in patients with moderate or severe hepatic impairment • Use in pregnant women • Long-term safety	Annual Reports Final Report	31 December 2021/2022/ 2023/2024 31 December 2025

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; 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; LFT: liver function test; MA: market authorisation; PASS: post-authorisation safety study; PD: pharmacodynamics; PV: pharmacovigilance; Study 105: VX17-445-105

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Susceptibility for influenza virus infections	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) • PASS
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided. PL Sections 2 and 4 PL Sections 2 and 4 where expectations for LFT monitoring and detection of potential signs of liver problems are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) • PASS
Cataract	**Routine risk minimisation measures:** SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided. PL Section 2 PL Section 2 where expectations for eye examinations are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105)

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
Long-term safety	**Routine risk minimisation measures:** SmPC Section 4.8 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) • PASS
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:** • Study in patients with moderate hepatic impairment (Study 007) (for evaluation of use in patients with moderate hepatic impairment only) • PASS

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

2.7. Update of the Product information

As a consequence of this new indication and taking also into account minor changes introduced by the MAH, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: since the revised text proposed within the package leaflet (PL) is shorter, simpler, and nearly identical to the text that was successfully user-tested, this does not present a substantial change and therefore no new readability testing is included with this submission.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which and at present, there is no cure. Cystic fibrosis is caused by mutations in the CFTR gene that result in 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. Lung disease is the primary cause of morbidity and mortality in people with CF. *F508del*, is the most common disease-causing mutation (84.7% of the individuals in the US and 81.1% of the individuals in Europe)[4],[5].

3.1.2. Available therapies and unmet medical need

Two types of CF therapies are currently authorised. The use of CF therapies that target the symptoms of the disease (such as nutritional supplements, antibiotics, and mucolytics), in combination with CFTR modulators (i.e. correctors and potentiators) is recommended to maintain and improve lung function, reduce the risk of infections and exacerbations; and improve quality of life.

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

Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA), Symkevi (tezacaftor/ivacaftor, TEZ/IVA) and Kaftrio (elexacaftor/tezacaftor/ivacaftor, ELX/TEZ/IVA) are CFTR modulators approved for CF patients with specific mutations.

The claimed indication by the MAH is as follows: "Kaftrio (ELX/TEZ/IVA) is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene."

This proposed indication covers the F/F genotypes and F/MF 'minimal function' genotypes in which Kaftrio is already approved. However, this broad indication would also include the F/G 'gating' genotypes and F/RF 'residual function' genotypes in which, approved modulator therapies are available

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

(IVA and TEZ/IVA). Nevertheless, these treatments do not cure the disease, and more efficacious treatments could fulfil this gap in these patients.

3.1.3. Main clinical studies

The main evidence for the efficacy of Kaftrio was presented in the marketing authorisation application, for heterozygous patients with minimal function mutations (F/MF (study 102) and F/F homozygous patients (study 103) and the follow-up study 105. The main evidence for the extension of the indication to a broad population of patients with at least one F508del allele is obtained from one clinical trial, study 104, where heterozygous patients with additional type of mutations are studied; patients with gating mutations (F/G) and patients with residual function mutations (RF).

Study 104 in CF patients 12 years and older is an 8-week randomized, double-blind, controlled study in subjects heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF genotypes). A total of 258 subjects received at least one dose of study drug. Ivacaftor was used as control treatment in patients with an F/G genotype and tezacaftor/ivacaftor in patients with an F/RF genotype. The primary endpoint was the absolute change in ppFEV1 from baseline for the ELX/TEZ/IVA group (within-group change).

ppFEV1 as a surrogate endpoint is a well-established endpoint, and a reduction in the decline of FEV1 is related to improved survival.

Pulmonary exacerbations and decline of lung function have an impact on survival in cystic fibrosis and reduce health-related quality of life. Preservation of lung function alongside reductions of the rate of pulmonary exacerbations are the main goals of treatment of cystic fibrosis.

3.2. Favourable effects

CF patients included in study 104 (both F/G and F/RF)
ELX/TEZ/IVA showed an absolute within-group change in ppFEV1 from baseline through week 8 of ELX/IVA/TEZ group of 3.7% (95% CI: 2.8, 4.6; p<0.0001). The FEV1 absolute change in ppFEV1 compared to the control group was a key secondary endpoint. The result of this analysis was consistent with the within-group changes (95% CI: 3.5%; 2.2, 4.7; p<0.0001).

The absolute within-group change in SwCl from baseline through week 8 of ELX/IVA/TEZ was -22.3 (95% CI: -24.5, -20.2; p<0.0001). The SwCl comparison with the control group resulted in a reduction of 23.1 mmol/L (95% CI: -26.1, -20.1; p<0.0001).

For the CFQ-R RD score, the within-group difference was an increase in score of 10.3 points (95% CI: 8.0, 12.7; nominal p<0.0001) and compared to the control group the treatment with ELX/TEZ/IVA resulted in an increase of 8.7 points (95% CI: 5.3, 12.1; nominal p<0.0001).

Consistent and significant benefits in ppFEV1 favouring ELX/TEZ/IVA were observed across all prespecified subgroups: age, sex, comparator group, baseline lung function, and geographic region.

In all cases, the percentage of responders (ppFEV ≥ 2.5%, SwCL <30 mmol/L, CFQ-R RD change ≥ 4 points) was higher in the ELX/TEZ/IVA group than in the control group, and the differences between the treatment groups were substantial.

CF patients 12 year and older with F/G genotype
Ad-hoc subgroup analyses were performed in the comparator subgroups, which are based on the two different genotypes included in the study. In the F/G population, the between-group data showed a beneficial change of ELX/TEZ/IVA treatment in ppFEV1 of 5.8 percentage point (95% CI: 3.5, 8.0;

nominal p<0.0001), in SwCL of -20.0 mmol/L (95% CI: -25.4, -14.6; nominal p<0.0001) and in CFQ-RD of 8.9 points (95% CI: 3.8, 14.0; nominal p=0.0008) compared to IVA monotherapy.

CF patients 12 years and older with F/RF genotype
The patients with an F/RF genotype were also analysed as an ad-hoc subgroup. The between-group data showed a beneficial change of ELX/TEZ/IVA treatment in ppFEV1 of 2.0 percentage point (95% CI: 0.5, 3.4; nominal p=0.0093), in SwCL of -24.8 mmol/L (95% CI: -28.4, -21.2; nominal p<0.0001) and in CFQ-RD of 8.5 points (95% CI: 4.0, 13.1; nominal p=0.0003) compared to TEZ/IVA combination therapy.

Several additional analyses were provided, including COVID-19 sensitivity analyses and subgroup analyses per comparator subgroup, analyses based on experienced or naïve CFTR modulator patients, and analyses in subsets of specific mutations. Also, more recent registry data were provided. All these additional analyses resulted in consistent outcomes compared to the outcomes as presented above.

3.3. Uncertainties and limitations about favourable effects

CF patients included in study 104 (both F/G and RF)
The study is not powered for between-group comparisons, but a formal between-group comparison is made. The subgroup analyses for the F/G and F/RF genotypes separately are performed ad-hoc. Efficacy data are based on study 104 of 8 weeks duration. The sustained effect of ELX/TEZ/IVA has been previously shown in in study 102 and the long-term open-label extension study 105. Long term efficacy data for F/R and F/G patients are provided based on study 110 but remain limited.

Due to the COVID-19 pandemic, also home assessments of FEV1 and CFQ-R were permitted. This introduces limitations, but the approach is reasonable based on the unforeseen circumstances.

3.4. Unfavourable effects

ELX/TEZ/IVA was generally well tolerated; 88 (66.7%) subjects in the ELX/TEZ/IVA group and 83 (65.9%) subjects in the control group experienced at least one AE, with only five (3.8%) subjects in the ELX/TEZ/IVA group and 4 (3.2%) subjects in the control group had severe AEs.

The most common AEs (occurring in ≥5% of subjects) in the ELX/TEZ/IVA group were headache, ALT increased, AST increased, and abdominal pain. The most common AEs (occurring in ≥5% of subjects) in the control group were headache, cough, infective PEx of CF, nausea, sputum increased, and diarrhoea.

Five (3.8%) subjects in the ELX/TEZ/IVA group and 11 (8.7%) subjects in the control group had SAEs. Infective PEx of CF occurred in 2 (1.5%) subjects in the ELX/TEZ/IVA group and 7 (5.6%) subjects in the control group; all other SAEs occurred in no more than one subject per treatment group. There were no life-threatening AEs and no deaths.

One (0.8%) subject in the ELX/TEZ/IVA group had AEs that led to study drug discontinuation (ALT increased and AST increased), and 2 (1.6%) subjects in the control group had AEs that led to study drug discontinuation (1 subject with an SAE of infective PEx of CF and 1 subject with SAEs in the SOC of psychiatric disorders). Five (3.8%) subjects in the ELX/TEZ/IVA group and 3 (2.4%) subjects in the control group had AEs that led to treatment interruption.

Rash events (AESI of rash) occurred in 4 (3.0%) subjects in the ELX/TEZ/IVA group and 5 (4.0%) subjects in the control group. In the ELX/TEZ/IVA group, one subject with rash event was male, and 3

subjects with rash events were female, none of whom were taking hormonal therapy. All rash events in the ELX/TEZ/IVA group were mild or moderate in severity.

Eight (6.1%) subjects in the ELX/TEZ/IVA group and one (0.8%) subject in the control group had an AESI of elevated transaminases; the majority of events were mild or moderate in severity, and none were SAEs. One (0.8%) subject discontinued ELX/TEZ/IVA treatment due to AEs of ALT increased and AST increased.
In the ELX/TEZ/IVA group, ALT or AST >3, >5, and >8 × ULN occurred in 4 (3.2%), 1 (0.8%), and 1 (0.8%) subject(s), respectively. In the control group, ALT or AST >3, >5, and >8 × ULN occurred in 2 (1.6%), 1 (0.8%), and 0 subject(s), respectively. o No subject had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN.

Two (1.5%) subjects in the ELX/TEZ/IVA group had AEs of blood creatine phosphokinase increased. Neither AE was serious or resulted in ELX/TEZ/IVA treatment discontinuation or interruption.

Mean SBP and DBP increased in the ELX/TEZ/IVA group. The largest mean (SD) increase in SBP from baseline was 3.0 (12.4) mm Hg (at Week 8) and the largest mean (SD) increase in DBP was 2.5 (8.9) mm Hg (at Week 8). No subjects had AEs related to increased blood pressure.

A total of 9 adolescents were enrolled in the control group and 15 adolescents in the ELX/TEZ/IVA group. The safety was generally consistent with the overall study population.

3.5. Uncertainties and limitations about unfavourable effects

Study 104 provides safety data on ELX/TEZ/IVA in F/G and F/RF patients for up to 8 weeks. There are no further data provided with this variation application regarding longer-term safety. However, there are controlled safety data from Study 102 (in F/MF) up to week 24 and Study 105 open-label extension interim analysis data (both F/F and F/MF) (271 subjects had an exposure of ≥48 weeks), which can be used to support the longer-term safety in patients with F/G and F/RF genotypes. Additionally, the MAH was requested to amend the planned Post authorisation safety study to include patients with F/RF and F/G mutation in order to further characterise safety in the post approval setting.

Study 104 is unusual in that both F/G and F/RF genotypes were combined and randomised as one group. No comparison of safety between F/G and F/RF genotypes has been provided. However, there is an overall low incidence of severe AEs, SAEs, AEs leading to low discontinuation across both the combined treatment group and combined control group, and no life-threatening AEs or AEs leading to death in either group. Therefore, it is considered that a sub-analysis by genotype group (F/G and F/RF) for safety would be of limited value. The safety data and AE profile from the combined F/G and F/RF group are also consistent with those in both F/F and F/MF genotype groups, and it is not anticipated that there would be a difference in safety in F/G versus F/RF genotypes.

3.6. Effects Table

Table 43 Kaftrio in the treatment of patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutation (data cut-off: 30 June 2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ppFEV1	Change 0-8 weeks LSM (95% CI)	%	3.7 (2.8, 4.6)	0.2 (-0.7, 1.1)	**SoE:** 3.5 (2.2, 4.7); p<0.0001 **Unc:** primary endpoint is within-group; comparator subgroups ad-hoc	*study 104
Sweat Chloride	Change 0-8 weeks LSM (95% CI)	Mmol/L	-22.3 (-24.5, -20.2)	0.7 (-1.4, 2.8)	**SoE:** -23.1 (-26.1, -20.1); p<0.0001 **Unc:** comparator subgroups ad-hoc	*study 104
CFQ-R RD	Change 0-8 weeks LSM (95% CI)	points	10.3 (8.0, 12.7)	1.6 (-0.8, 4.1)	**SoE:** 8.7 (5.3, 12.1); nominal p<0.0001) **Unc:** comparator subgroups ad-hoc	*study 104
Unfavourable Effects						
Headache		%	8.3	15.1	**Unc**: Limited size of the data set	*study 104
Diarrhoea		%	3.8	6.3		*study 104
Abdominal pain		%	5.3	1.6		* study 104
ALT	ALT increased	%	6.1	0		* study 104
AST	AST increased	%	6.1	0		* study 104

Abbreviations: ALT alanine transaminase; AST aspartate transaminase;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The submitted F/any indication was based on the hypothesis that Kaftrio mainly acts though the *F508del* allele and that all patients with an *F508del* allele could be included in the indication. During the initial marketing authorisation assessment, the effects in the F/MF population and all additionally provided information made it plausible, but not definitively conclusive that the ELX/TEZ/IVA mainly acts through the *F508del* allele and would result in a benefit in all patients with at least one *F508del* allele. A study in F/RF or F/G patients was considered required to determine the added benefit of the triple combination over approved IVA and TEZ/IVA and further assess the MAH hypothesis. Clinical data from study 104 are provided in this application in the F/RF and F/G patients for whom other CFTR modulators are already approved.

According to the MAH, if a modulator has a large effect on the *F508del-CFTR*, then the presence of a single *F508del* allele would be sufficient to derive a clinical benefit. Based on this hypothesis and the results from studies 102 and 103, a broad indication was initially proposed to include all patients with at least one *F508del* mutation independently of the second allele. This meant that efficacy for non-tested populations of F/MF, F/RF and F/G should be extrapolated.

Importance of the favourable effects

The observed difference of 3.5 percentage points (p<0.0001) between ELX/TEZ/IVA and the control group in an absolute change of ppFEV1 is well above the predefined threshold (3%, to have >99% of power).

Separate F/G and F/RF efficacy outcomes are important to be determined as these populations usually have a different CF severity and because the standard CFTR modulator is different. In F/G patients and F/RF patients, a difference of 5.8 percentage points ($p<0.0001$) and 2.0 percentage points ($p<0.0093$) were seen compared to IVA and TEZ/IVA, respectively.

Considering the natural evolution of the disease in CF patients in study 104, the observed effect is considered clinically relevant (see below).

Strength of the evidence
Consistent improvements in ppFEV1 favouring ELX/TEZ/IVA were observed across the prespecified subgroups. The results of the primary parameter are supported by all key secondary parameters. CFQ-R respiratory domain and sweat chloride both showed improvements above the Minimum Clinically important Difference (MCID). Also, in the comparator subgroups (F/RF and F/G populations) the CFQ-R respiratory domain and sweat chloride both showed improvements well above the MCID.

Impact of the uncertainties
The comparator subgroups were tested ad-hoc, but still able to provide a good effect size for the efficacy parameters over the control groups.

The overall clinical benefit seen on ppFEV1, SwCL and CFQ-R with ELX/TEZ/IVA in the F/RF and F/G patients has such a large effects sizes, that it is unlikely that uncertainties related to for example sensitivity analyses and previous modulator use will affect the data in such an extent that this benefit could be questioned.

The study duration was only 8-weeks. However, the sustained effect of ELX/TEZ/IVA has been sufficiently shown in study 102 and the long-term open-label extension study 105 in the initial MAA.

Safety

ELX/TEZ/IVA was generally safe and well-tolerated for 8 weeks. The safety results appear consistent with the safety established in the clinical development program in the initial ELX/TEZ/IVA MAA. No new safety concerns were identified, but the new safety set is relatively small. Safety will be further characterised in the safety study to be conducted post approval as previously agreed at time of the initial marketing authorisation.

3.7.2. Balance of benefits and risks

Efficacy
In the overall population (F/G and F/RF), a clinical benefit is demonstrated for the primary and secondary endpoints. Due to differences in severity and standard of care, the two separate subpopulations (F/RF and F/G) are considered equally important.

For CF patients with the F/G genotype, the IVA-controlled part of the study provided efficacy data that demonstrate that ELX/TEZ/IVA provides a substantial clinical benefit, both in the primary and the key secondary endpoints. These results are considered robust and clinically relevant.

For CF patients with the F/RF genotype, the TEZ/IVA controlled part of the study provided efficacy data demonstrating substantial clinical benefit of ELX/TEZ/IVA both in the primary and the (key) secondary endpoints. The results are regarded as clinically relevant for both populations.

To identify the robustness of the effect and see whether different gating and residual function mutations might influence the effect size, it is of interest to see the clinical benefit in a subset based on specific mutations. In study 104, patients representing a total of 24 mutations (RF and G) were recruited, 12 F/RFs and 7 F/Gs were represented (with at least one patient) in the ELX/TEZ/IVA

treatment group; the remaining 5 were treated with appropriate control. Information on additional mutations were also provided from study 110 and the real-world effectiveness registry data. For almost all of the genotypes included in both the F/G and F/RF categories, clinical benefit is observed, and in most cases, it can be considered clinically meaningful. Overall, the CHMP considered that the totality of the data provides sufficient information on patients with F/RF and F/G mutations but also to conclude that Kaftrio provides efficacy in patients with at least one *F508del* mutation.

Indication

Overall, Kaftrio is currently approved for F/F and F/MF mutations and demonstration of efficacy has been demonstrated in F/RF and F/G patients as discussed in this application. The CHMP therefore agreed with the applicant, that hypothesis of efficacy based at least a F508Del mutation on one allele is demonstrated and considered the below broad indication approvable:

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Safety

ELX/TEZ/IVA was generally safe and well-tolerated for 8 weeks. The safety results appear consistent with the safety established in the clinical development program in the initial ELX/TEZ/IVA marketing authorisation. No new safety concerns were identified. As a consequence of this extension of indication the MAH was requested to update the planned PASS to include also patients with F/FR and F/G mutations.

3.8. Conclusions

The overall Benefit/Risk of Kaftrio is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 indication of Kaftrio to patients with Cystic Fibrosis aged 12 years and older who have at least one F508del mutation in the CFTR gene, regardless of the second allele, based on the results of Study VX18-445-104 in CF patients 12 years and older. This is an 8-week randomized, double-blind, controlled study in subjects heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF genotypes). Changes were also made to the PI to bring it in line with the

current Agency/QRD template.

As a consequence of this new indication and QRD changes, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The RMP is updated to version 2.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-002324-PIP01-17 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

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

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Kaftrio EMEA/H/C/005269/II/0001

Attachments

1. SmPC and Package Leaflet with changes highlighted as adopted by the CHMP on 25 March 2021.

Appendix

1. CHMP AR on similarity dated 25 March 2021