EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2021
EMA/206661/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0089

Note

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

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List of abbreviations

Abbreviation	Term
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 and IIIB

Extension of indication to extend the indication of Kalydeco (ivacaftor) tablets in combination regimen with Kaftrio (ivacaftor/tezacaftor/elexacaftor) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene; as a consequence, sections 4.1, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.2 of the RMP has also been submitted.

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

Information relating to orphan designation

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 8 July 2008. Kalydeco was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis (CF).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0163/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0163/2020 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: Maria Concepcion Prieto Yerro Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur's preliminary assessment report circulated on:	18 November 2020
PRAC Rapporteur's preliminary assessment report circulated on:	13 November 2020
PRAC outcome adopted on:	26 November 2020
Joint Rapporteur's updated assessment report circulated on:	6 December 2020
Request for supplementary information adopted by the CHMP on:	10 December 2020
MAH's responses submitted to the CHMP on:	21 January 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 February 2021
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2021
PRAC RMP advice and assessment overview adopted by PRAC	11 March 2021
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 March 2021
CHMP opinion:	25 March 2021
The CHMP adopted a report on similarity of Kalydeco with TOBI Podhaler, Bronchitol, Symkevi and Kaftrio on date (Appendix 1):	25 March 2021

2. Scientific discussion

2.1. Introduction

Kalydeco is approved in the EU in a combination regimen with Kaftrio (elexacaftor/tezacaftor/ivacaftor; ELX/TEZ/IVA) to treat 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.

This Type II variation application seeks to expand the indication of Kalydeco in combination with 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 *CFTR* allele (F/any). This application was supported by Study 104, a Phase 3 randomized, double-blind, multicenter study of ELX/TEZ/IVA compared to either IVA or TEZ/IVA in subjects who have an *F508del* mutation on 1 allele and either a gating (F/Gating) or residual function (F/RF) mutation on the other allele. For patients with these genotypes, the non-*F508del* allele is responsive to an approved CFTR modulator: Kalydeco (IVA monotherapy, tablets) is approved to treat patients with gating mutations (10 mutations indicated), and Symkevi (TEZ/IVA) is approved to treat patients with F/RF genotypes (14 F/RF genotypes indicated).

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

The claimed indication is as follows:

Kalydeco tablets are indicated in a combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1).

The most common mutation is the *F508del* mutation. Therefore, the claimed indication would cover the majority of the CF population even though the genetic diversity of the European CF population is higher, with more people without an *F508del* mutation on either allele. The frequency of the *F508del* mutation ranges from 60 to > 80% of CF alleles in Northern European countries down to < 40 to 60% in southern European regions (De Boeck K, Lee T, Amaral M, et al. Cystic fibrosis drug trial design in the era of CFTR modulators associated with substantial clinical benefit: stakeholders' consensus view. J Cyst Fibros 2020;19(5):688-695).

Epidemiology

Cystic fibrosis affects approximately 30,000 individuals in the United States (US)[1] and a total of 42,000 in the EU (excluding the data from Russia, Turkey and Israel)[2]. The incidence and prevalence of CF vary between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.

The prevalence of certain CF complications varies according to the age group. Exocrine pancreatic insufficiency is often already present from birth or develops in infancy. CF related liver cirrhosis clinically presents most frequently between the ages of 5 to 15 years, but with a lower frequency in the third decade. CF related pulmonary disease mostly starts in childhood. CF related diabetes often starts to develop in patients around the age of 10 years and may progress in severity over years to insulin dependency. Lung disease is the primary cause of morbidity and mortality in CF.

The current life expectancy is > 30 years. The ageing of the CF population has brought a paradigm shift in outlook in the adult healthcare sector, from a focus on the care of lung disease to the management of a complex multi-system chronic illness, including the care for diabetes, renal function, osteoporosis, and hepatic function.

Data in the literature suggest that early therapeutic intervention is beneficial to young children with CF; studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed by newborn screening.

Biologic features

CFTR mutations can be classified according to the mechanisms by which they disrupt *CFTR* function. Stop codon mutations (class I) result in a truncated non-functional *CFTR*, class II mutations consist of aberrantly folded *CFTR* protein that is degraded by the cell quality control system, while class III mutations lead to defective regulation of the *CFTR* protein and, consequently, the absence of *CFTR* function. These three classes usually lead to a classic CF phenotype with pancreatic insufficiency. *CFTR* mutations that lead to defective chloride conductance are grouped together in class IV. Class V mutations interfere with normal transcription, thereby reducing the amount of otherwise normal *CFTR*. These latter two classes are mostly associated with a milder expression of the disease.

CF-causing mutations can be divided into 2 groups based on the extent of loss of chloride transport caused by the mutation. A complete or near complete loss of *CFTR* chloride transport is referred to as "minimal function" of *CFTR*. A less complete loss of CFTR-mediated chloride transport is referred to as "residual function" of *CFTR*.

The classic or typical form of CF is diagnosed if a patient demonstrates clinical disease in one or more organ systems and has elevated sweat chloride (≥60 mmol/L). Most of these patients have disease manifestations in multiple organ systems (pancreas, upper and lower respiratory tract, and male reproductive tract). There is a wide spectrum of severity in CF, even among patients who have the same genotype. Some patients are severely affected, with symptoms already present at birth (meconium ileus). Most patients develop symptoms during childhood, while some patients may only demonstrate mild or atypical symptoms in adulthood. Usually, patients with class I-III mutations are more severely affected than those with other class mutations.

Clinical presentation and diagnosis

The disease phenotype differs considerably among patients, even among patients with the same genotype. The CFTR genotype primarily determines the degree of pancreatic exocrine dysfunction, sweat chloride concentration and malformation of the male reproductive tract. However, factors independent of the CFTR genotype are responsible for variation in lung disease, the primary cause of morbidity and mortality in CF. In lung disease, environmental factors, socio-economic factors and also the presence of modifier genes play an important role. Lung disease is the primary cause of morbidity and mortality in people with CF. However, CF is a systemic disease and complications such as cystic fibrosis-related diabetes and cystic fibrosis-related liver disease have emerged as important causes of morbi-mortality which are usually present in the paediatric age.

Management

Most treatments available for the treatment of CF are symptomatic, but the CFTR modulators may improve CFTR function, which is believed to be the primary cause of disease. Current treatment guidelines recommend CFTR modulator and symptomatic medications concomitantly administered to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

2.1.2. About the product

In the EU, Kalydeco is indicated in monotherapy for patients with certain pre-specified gating (class III) mutations as well as for those with the *R117H-CFTR* mutation. Kalydeco is also indicated in a combination regimen with tezacaftor /ivacaftor for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who are homozygous for the *F508del* mutation or who

are heterozygous for the *F508del* mutation and have one of the following mutations of residual function in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* It is also indicated in combination with elexacaftor/tecazaftor/ivacaftor for the treatment of adult and adolescents 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.

The scope of the present application is to extend the indication of Kalydeco (tablets) in combination with Kaftrio for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one *F508del* mutation in the *CFTR* gene.

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

This application consisted of results from clinical study 104. No specific advice was requested/provided in relation to this study in heterozygous *F508del* patients with a second mutation of residual function (F/RF) or with defective gating (F/G).

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

This application was supported by results from Study VX18-445-104 (study 104), 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).

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.

2.3.2. Pharmacokinetics

The pre-dose concentration values of each analyte (ELX, TEZ, IVA, and relevant metabolites) were measured in study 104 and presented as summary statistics by treatment group and for individual concentrations (Table 1). 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 1 Summary of Pre-dose Concentrations (Ctrough) by Visit for Plasma Analytes.

Treatment Group / Analyte	Visit and Statistic											
	Day 1			Day 15			Week 4			Week 8		
	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

2.3.3. Pharmacodynamics

No new data relevant to this indication in combination with Kaftrio has been provided which was considered acceptable.

2.3.4. PK/PD modelling

No new data relevant to this indication in combination with Kaftrio has been provided which was considered acceptable.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of Kalydeco in combination with Kaftrio has been adequately investigated.

The MAH 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. Furthermore, exposures of all analytes were consistent with those observed in previous ELX/TEZ/IVA studies 102 and 103.

No additional data are required to support this application.

2.3.6. Conclusions on clinical pharmacology

Overall, the pharmacokinetics and pharmacodynamics of Kalydeco in combination with Kaftrio have been adequately investigated and are correctly reflected in the SmPC.

2.4. Clinical efficacy

To support this type II variation, the MAH submitted the results of Study VX18-445-104 (study 104), a phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of Kaftrio in combination with Kalydeco 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). In addition, supportive efficacy data from Study 110, a Phase 3, open-label study evaluating the long-term safety and efficacy of VX-445 combination therapy in subjects with CF who are heterozygous for the F508del mutation and a gating or residual function mutation (F/G and F/RF Genotypes) were also submitted.

2.4.1. Dose response study

No new data relevant to this indication in combination with Kaftrio has been provided which is considered acceptable.

2.4.2. Main study

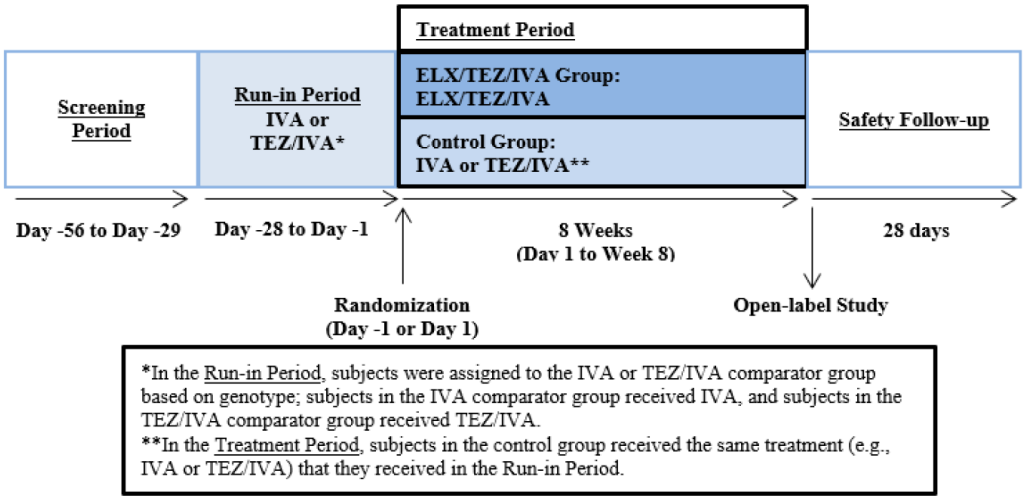
Title of Study

VX18-445-104 (study 104): 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, randomized, 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 2). After completing the run-in subjects were randomized (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 2 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 ppFEV1 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.

Twenty-four mutations (10 gating mutations and 14 residual function mutations) were eligible for recruitment at EU sites, in line with the approved indications for IVA and TEZ/IVA in the EU. However, as other regions have different but overlapping approved lists of genotypes/mutations approved for Tezacaftor/Ivacaftor and Ivacaftor, different lists of eligible genotypes were applied in the different

regions. Study wide, 38 mutations (see Table 2) were considered eligible: 12 gating mutations, and 26 residual function mutations.

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) ≥3xULN
    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.
4. Use of prohibited medications within the specified window before the first dose of study drug in the Run-in Period (Day -28), (Table 3).

Table 3 Prohibited medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed after the first dose of study drug on Day -28	None allowed through completion of study participation	ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, was prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed after the first dose of study drug on Day -28	None allowed through completion of study participation	
Non-Vertex CFTR modulators (investigational or approved)	None allowed within 28 days or 5 terminal half-lives (whichever was longer) before screening	None allowed through completion of study participation	These agents may confound the results of this study and were therefore prohibited.
Vertex CFTR modulators (investigational or approved), except for study drugs	None allowed from the first dose of study drug on Day -28	None allowed until after the last dose of study drug	These agents may confound the results of this study and were therefore prohibited.

ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

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

Treatments

In the open-label Run-in Period, subjects were assigned to the IVA or TEZ/IVA comparator group based on F/G or F/RF genotype. During the Run-in Period, subjects in the IVA (F/G patients) comparator group received IVA 150 mg every 12 hours (q12h) and subjects in the TEZ/IVA (F/RF patients) comparator group received TEZ 100 mg once daily (qd)/IVA 150 mg q12h. After completing the Run-in Period, subjects were randomized 1:1 to the ELX/TEZ/IVA or control group.

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:

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:

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.

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 randomized 1:1 to either the ELX/TEZ/IVA group or the control group. Randomization 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 foetus 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) randomization 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 organization (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 minimize risk to COVID-19 exposure. The MAH confirmed that this was prior to database lock. Key changes to analyses in Version 1.0 of the SAP (06 March 2020) are summarized in Table 5.

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.

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

Analysis sets

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

The All Subjects Set included all subjects who were randomized or received at least 1 dose of study drug. This analysis set was used for all individual subject data listings and disposition summary tables, unless otherwise specified.

The FAS included all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug in the Treatment Period. The FAS was used to summarize subject demographics and baseline characteristics, and for all efficacy analyses in which subjects were analysed according to their randomized treatment group, unless otherwise specified.

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

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

Analysis methods

Unless otherwise defined, all efficacy analyses described in this section were based on the FAS.

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

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 model included treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV1, continuous baseline SwCl, and comparator group (IVA comparator versus TEZ/IVA comparator) as covariates. The Day 15 Visit was not included in the estimation of the average treatment effect through Week 8. The model was estimated using restricted maximum likelihood. Denominator degrees of freedom for the F-test for fixed effects was estimated using the Kenward-Roger approximation. An unstructured covariance structure was used to model the within-subject errors. Conditional on the observed data and covariates, missing data were assumed to be missing at random; consequently, no imputation of missing data were to be performed.

The primary results 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. The adjusted means with 2-sided 95% confidence intervals and 2-sided P values were provided. Furthermore, the within-group treatment difference at each post-baseline visit were also provided, obtained from the model. The adjusted mean (with SE) obtained from the MMRM analysis at each post-baseline visit up to Week 8 was plotted by treatment group.

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

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 have missing changes in ppFEV1 at Week 8 in any treatment group.

For the secondary endpoints, Absolute change in SwCl 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 and Absolute change in SwCl from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group analyses were to be based on the same MMRM model as the analysis of the primary endpoint.

Testing procedure

A hierarchical testing procedure was to be used to control the overall type I error rate at an alpha of 0.05 for the primary endpoint and the key secondary endpoints tested. The key secondary endpoints were only to be tested at an alpha of 0.05 if the primary endpoint of absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group was statistically significant. 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 testing order of the key secondary endpoints is as follows:

• First key secondary endpoint: Absolute change in SwCl from baseline through Week 8 for the ELX/TEZ/IVA group

• Second key secondary endpoint: Absolute change in ppFEV1 from baseline through Week 8 for the ELX/TEZ/IVA group compared to the control group

• Third key secondary endpoint: 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)

Disposition/Reason, n (%)	Control	ELX/TEZ/IVA	Total
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.

Recruitment

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

Study initiation date: 28 August 2019 (date first eligible subject signed the informed consent form)

Study completion date: 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; Absolute change in BMI from baseline at Week 8 was added as an exploratory endpoint to meet an FDA post-marketing commitment.

The MAH implemented safety measures to provide subjects with the opportunity to continue participation in Study 104 while ensuring their safety by minimizing 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 minimizing impact to study integrity. A summary of these measures pertinent to Study 104 are summarized in Table 7.

Table 7 Summary of implemented measures to minimize 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.

Important protocol deviations

There were 2 IPDs. Two patients were listed as meeting EC# 1(informed consent form), and both were discontinued during the run-in period before randomisation.

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)

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)

Characteristic	Control N = 126	ELX/TEZ/IVA N = 132	Total N = 258
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 for Kaftrio. 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. **Error! Reference source not found.**Table 11 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.

Breakdown of the non F allele (RF or G)

Of the 38 eligible second mutations eligible for the study globally, 24 were in the end enrolled; 14 of these were RF mutations, and 10 were G mutations. Only one mutation (in one patient) was recruited that was 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 presents the genotypes of subjects in the FAS by comparator group and treatment group.

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

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

In total 13 patients of the 271 subjects in the All Subjects Set were excluded from the efficacy analysis, as they did not reach randomisation: these included the 12 discontinuations previously listed, or as in the case of one patient who was randomised but was not treated in the treatment period due to an AE. 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 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%).

See participant's flow section above.

Outcomes and estimation

Primary Endpoint

The study met its primary endpoint; there was a within group absolute improvement of 3.7 pp FEV1 (95% CI: 2.8, 4.6; P<0.0001) from baseline for the ELX/TEZ/IVA group though week 8 (Table 14).

Table 14 MMRM Analysis of Absolute Change From Baseline in ppFEV1 Through Week 8 for the ELX/TEZ/IVA Group (FAS)

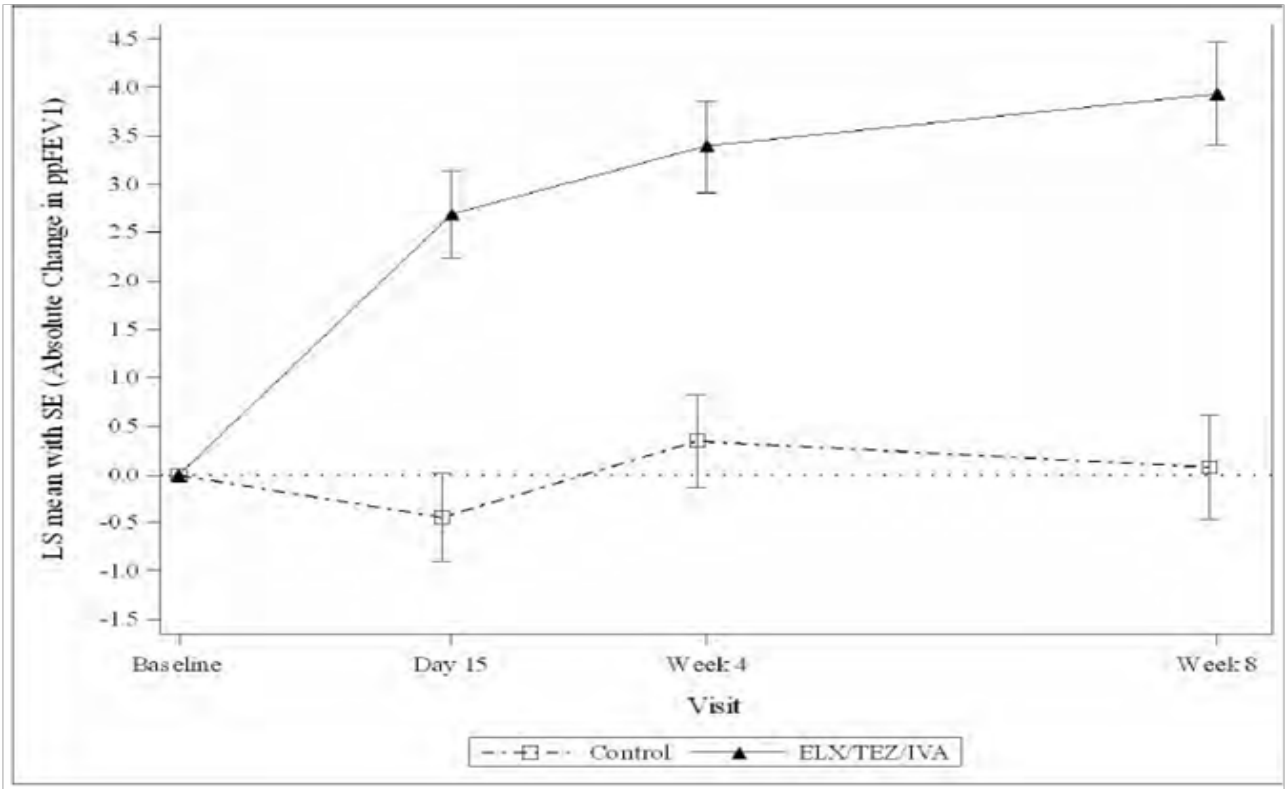
	ELX/TEZ/IVA N = 132
Baseline	
n	132
Mean (SD)	67.1 (15.7)
Absolute change through Week 8	
n	115
LS mean (SE)	3.7 (0.5)
95% CI of LS mean	(2.8, 4.6)
P value within treatment	<0.0001

Source: Table 14.2.1.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; 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.

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



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.

A sensitivity analysis was performed using the multiple imputation method to assess the impact of missing data; and results were consistent with the primary analysis. An additional pre-specified analysis was performed that included home-assessed spirometry (i.e., spirometry assessed independently by the subjects at home). The results for the through Week 8 endpoint were consistent with the primary analysis, i.e., the LS mean within-group absolute change in ppFEV1 was 3.8 (95%CI: 2.9, 4.7).

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).

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

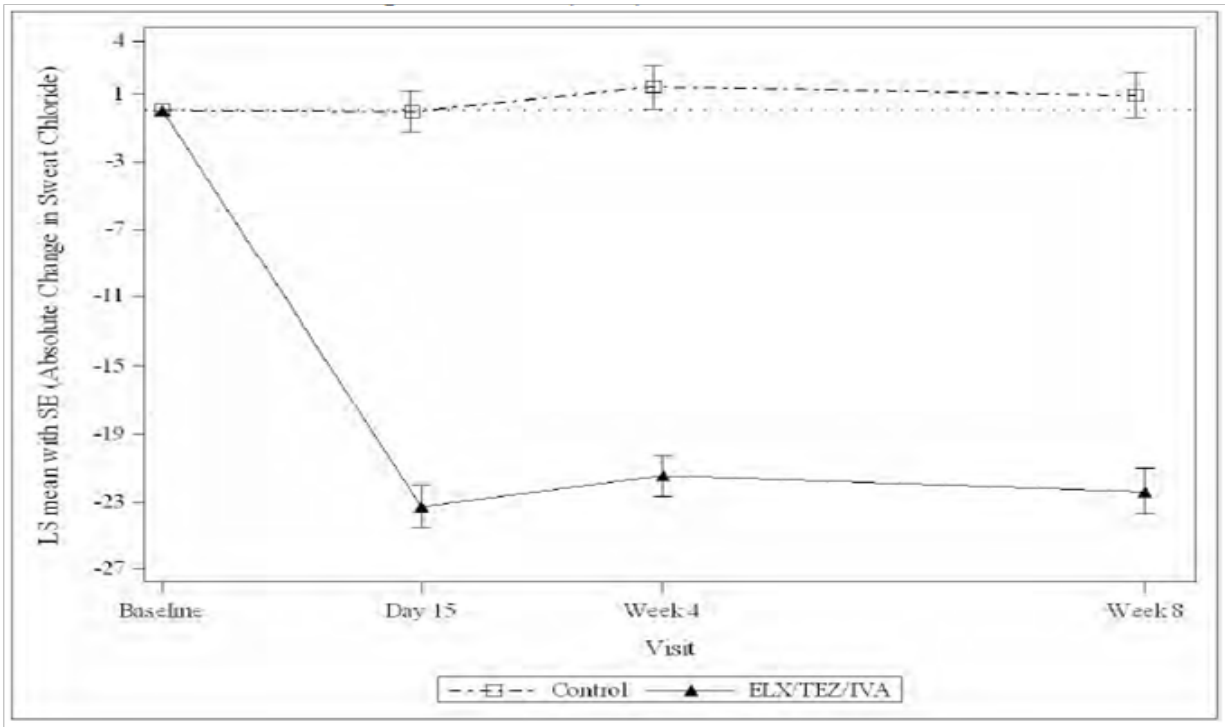
Key secondary endpoints

- **Absolute change in SwCl from baseline through Week 8**

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), see Figure 3. ELX/TEZ/IVA treatment also resulted in a statistically significant improvement in sweat chloride through Week 8 compared to the control group, with an LS mean treatment difference of -23.1 mmol/L (95% CI: -26.1, -20.1; P<0.0001).

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.

- **Respiratory domain (RD) of CFQ-R**

This and other secondary endpoints were not controlled for multiplicity, thus the p values are nominal.

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). 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). 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.

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 shown.

For each parameter, the percentage of subjects reaching the specified threshold was substantially higher in the ELX/TEZ/IVA group than in the control group. A majority of subjects who received ELX/TEZ/IVA had a change in ppFEV1 of ≥1.5 percentage points, a SwCl value <60 mmol/L (i.e., the

diagnostic threshold for CF), and/or a CFQ-R RD score that met or exceeded the minimum clinically important difference (MCID) of 4 points. Approximately 50% of subjects who received ELX/TEZ/IVA had a change in ppFEV1 of ≥2.5 percentage points and a SwCl value <30 mmol/L (i.e., the threshold concentration below which CF is considered unlikely). In the control group, a majority of subjects had a SwCl value <60 mmol/L; no other parameter thresholds were met by at least half of the subjects in the control group.

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

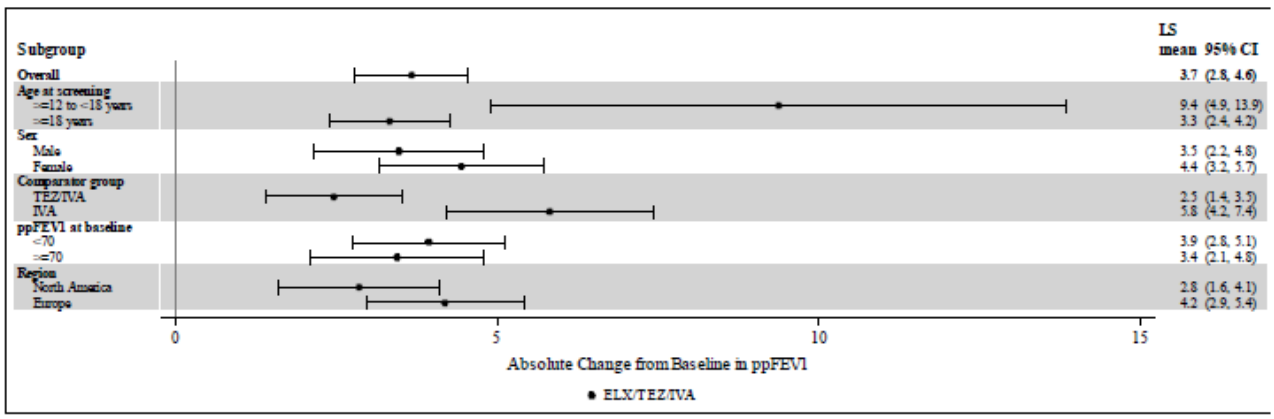
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; N1: number of subjects with non-missing value; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

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

Prespecified subgroup analyses of the primary efficacy endpoint, absolute change from baseline in ppFEV1 through Week 8 for the ELX/TEZ/IVA group, were performed are presented in Figure 4 below.

Figure 4 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: Figure 14.2.1.1

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

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.

Subgroup analyses for the key secondary and other secondary endpoints per comparator group are outlined in Table 16 Study 104 Comparator Group Subgroup Analyses, FAS.

Table 16 Study 104 Comparator Group Subgroup Analyses, FAS

	IVA Comparator Group (F/Gating)		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 **sweat chloride** 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

	IVA Comparator Group (F/Gating)		TEZ/IVA Comparator Group (F/RF)	
Statistic	IVA N = 45	ELX/TEZ/IVA N = 50	TEZ/IVA N = 81	ELX/TEZ/IVA N = 82
Absolute change from baseline in **sweat chloride** 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 14.1.4.1, Table 14.2.1.11, Table 14.2.2.7, Table 14.2.3.13, and Ad hoc Table 14.2.1.14

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

Lung function endpoints: ppFEV1

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). 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).

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). 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).

Respiratory domain of CFQ-R

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). 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). 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 group and treatment group 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

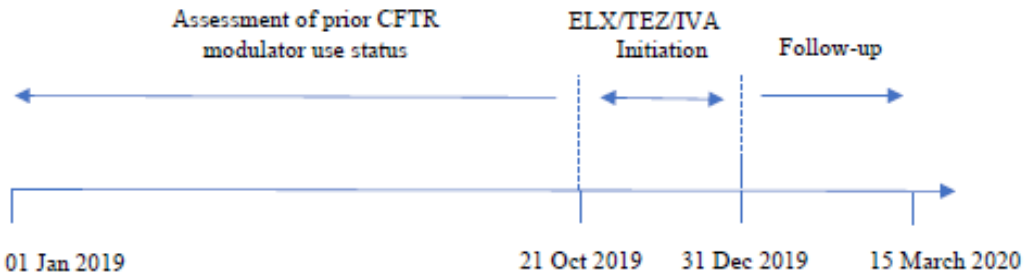
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N1: number of subjects with non-missing value; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

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

ppFEV1 data by genotype (Figure 5) were provided by the MAH upon request by CHMP. 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 5 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. The analysis presented in the Kaftrio MAA included ppFEV1 data from 297 patients (136 F/G and 161 F/RF), whereas data from 338 patients were provided in response to this recent query (157 F/G and 181 F/RF). 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. By-genotype analyses of SwCl and CFQ-R RD based on Study 104 and Study 110 data were presented upon request by CHMP.

Outcomes and Data Analysis

The data analysis approach was the same as the analysis presented in the initial Kaftrio MAA. The most recent measurement obtained within 90 days before ELX/TEZ/IVA treatment initiation served as the baseline value. The last measurement available in the period following therapy initiation on or 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 described in the initial Kaftrio MAA (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 initiated 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, there were 157 F/G patients who had a mean age of 31.8 years and a mean treatment duration of 66.6 days. There were 181 F/RF patients who had a mean age of 39.2 years and a mean treatment duration of 70.3 days. Consistent with the previous analysis, 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 or Study 110 data. Due to the limitations of RWE 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). Although there are no clinical study or real-world data to share for the other 13 genotypes at this time, the results of ELX/TEZ/IVA Phase 3 studies and CFFPR data can be extrapolated to these patients, because the Phase 3 studies collectively showed that patients with one copy of F508del derive benefit from ELX/TEZ/IVA treatment, regardless of their second CFTR allele.

Summary of main study

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

Table 21 Summary of Efficacy for 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)		
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:	8 weeks

	Duration of Run-in phase: Duration of Extension phase:		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%.

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. Results are preliminary; this study is ongoing. The study was not powered for this subgroup analysis of subjects at least 65 years of age.

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

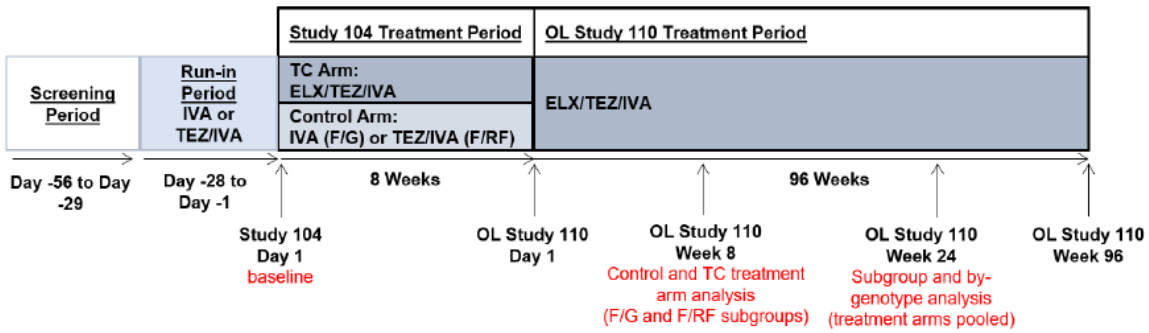
Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of Study 104. $ppFEV_1$ summary includes spirometry data obtained in clinic only. CFQ-R RD score summary includes both in-clinic and home-assessed data.

Supportive study

Study 110 is a Phase 3, open-label study evaluating the long-term safety and efficacy of VX-445 combination therapy in subjects with CF 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 6 summarises both analyses based on protocol Version 1.0.

Figure 6 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 analyzed 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.

The results for both Study 104's control group and Study 104's 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. 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		F/RF		Overall	
		IVA Comparator Group		TEZ/IVA Comparator Group			
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		F/RF		Overall	
		IVA Comparator Group		TEZ/IVA Comparator Group			
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		F/RF		Overall	
		IVA Comparator Group		TEZ/IVA Comparator Group			
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, 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. 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 MAA dossier (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 was included in the Kaftrio 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 when comparing 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 results in residual function; IVA: ivacaftor; LS: least square; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

2.4.3. Discussion on clinical efficacy

In this application, based on data in the F/RF and F/G populations from study 104, the MAH applied for the inclusion of the following indication in section 4.1 of Kalydeco SmPC:

Kalydeco tablets are indicated in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene.

Supportive data from study 110 and real-world data (from the US Cystic Fibrosis Foundation Patient Registry, CFFPR) from a post-authorisation setting were also provided.

Design and conduct of clinical studies

Efficacy and safety of Kalydeco in combination with Kaftrio 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 in the Kaftrio CHMP AR (EMEA/H/C/005269/0000) and led to the approval of Kaftrio in combination use with Kalydeco in F/F and F/MF CF patients. The current extension of indication was based on the results of study 104, a randomised, double-blind, controlled multicentre

study, designed to provide for prescribers and patients a quantification of the magnitude of clinical benefit derived from Kaftrio (VX-445/TEZ/IVA) in combination with Kalydeco in F/G and F/RF patients.

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.

Duration
The duration of the treatment period in study 104 was 8 weeks. Such treatment period is not in line with the Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (Doc. Ref. EMEA/CHMP/EWP/9147/2008-corr*). Furthermore, important parameters such as exacerbations, and BMI cannot be reliably measured in such short period. Nevertheless, the sustained effect of Kaftrio in combination with Kalydeco has been studied in F/G and F/RF patients in study 110 and 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, although uncontrolled. Considering the above, the current 8-week duration was considered acceptable by CHMP to evaluate the efficacy and safety of Kalydeco in combination with Kaftrio in the F/G and F/RF CF populations.

Inclusion and exclusion criteria
Overall, the inclusion and exclusion criteria were similar to the criteria for studies 102 and 103 (Kaftrio CHMP AR -EMEA/H/C/005269/0000). 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. In study 104, the CF diagnosis was confirmed by the investigator. Considering that all the subjects will have two disease causing mutations, the minimal sweat chloride value was not considered to be a prerequisite for the CF diagnosis. Therefore, the inclusion and exclusion criteria were considered acceptable by CHMP.

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 approved mutations for Kalydeco and Symkevi differ between the US and the EU, patients may have been included in the trial while their mutation is not included in the indications currently approved in the EU. This was the case for two gating mutations and 12 residual function mutations. However, only one of these mutations (*R347H* patients) was recruited in the trial and is described under the results section below. Therefore, the population included in the trial was overall considered representative of the Kalydeco and Symkevi approved European populations.

Endpoints
The primary endpoint was the absolute change in $ppFEV_1$ from baseline through Week 8 for the ELX/TEZ/IVA group in study 104. The comparison for $ppFEV_1$ to the control group (IVA and TEZ/IVA treatments) was made as a key secondary endpoint (step 3 in the confirmatory hierarchical testing procedure). Furthermore, the absolute changes from baseline in SwCL (both with and without comparison to the control group) were also included as key secondary endpoints. The primary and key secondary endpoints as well as the other secondary and exploratory efficacy endpoints such as CFQ-R score and BMI are accepted endpoints in CF clinical studies.

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. Upon request by CHMP, the MAH presented the requested subgroup analyses, however, these may be underpowered based on

the numbers in the subgroups. This is further discussed below (see discussion of the results). The same limitations as outlined above for the primary endpoints, also apply to the key secondary endpoints (FEV1 and SwCl). Moreover, the remaining following 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, home assessments of FEV1 and CFQ-R were permitted. Sensitivity analyses were provided to verify the results based on clinic data only or on clinic and home assessments data. Based on these unforeseen circumstances, this 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 $ppFEV_1$ and SwCL. These statistical analysis approaches are in line with the analyses used to support the initial approval of Kaftrio in combination with Kalydeco and are thus overall acceptable.

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 effect. 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**.**

Furthermore, the MAH summarised 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 categorised missing data causes into two categories. The missing at random assumption was considered plausible for category 2 missing data (including missed visits due to COVID) while missing not at random was considered more plausible for category 1 missing data.

Upon request by CHMP, he MAH presented sensitivity analyses for between-group comparisons of the absolute change in $ppFEV_1$ 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. The results of these sensitivity analyses are considered consistent with the primary analyses.

The trial was amended once, to include an absolute change in BMI from baseline at Week 8 as an exploratory endpoint. This amendment does not impact the entire conduct of the trial.

Efficacy data and additional analyses

Demographic and baseline characteristics were overall balanced between the two treatment groups in study 104. In addition, the demographic and baseline characteristics for each patient population were presented by the MAH (F/RF, TEZ/IVA comparator group and F/G, IVA comparator group) and were in general balanced between the two treatments.

The median weight, height and BMI for both treatment and control groups were matched, the overall mean BMI was 24.06 kg/m2 (range 15.81 to 44.36). The mean age of the patient population recruited

was older than the one recruited in the 2 pivotal trials of Kaftrio initial MA: the mean age for Studies 102 and 103 was in the mid-late 20s, whereas for study 104 there was a mean age of 37.7 years. Both genotype-based comparator groups in Study 104 were older, on average, than the F/G 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 was 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.

In terms of previous or baseline treatments, the groups were also overall similar (dornase alpha (52.3%), azithromycin (44.2%), inhaled antibiotic (40.7%), any bronchodilator (86.8%), inhaled hypertonic saline (43%). Overall the 2 groups were balanced for these prior therapies; any of the small differences were unlikely to be meaningful. For subgroups based on the control treatment IVA and TEZ/IVA, an imbalance was seen in the concomitant use of azithromycin in the F/G population (55.6% in the IVA group and 34.0% in the ELX/TEZ/IVA group). Considering all the other baseline parameters and concomitant medication that were very balanced between the IVA and ELX/TEZ/IVA group; it was considered unlikely that this imbalance was caused by a difference is CF severity between these groups.

In terms of baseline characteristics, the included populations might have a relatively milder CF severity, as opposed to the one that was included in the studies supporting the Symkevi and Kalydeco registration dossier; i.e. the SwCl values were lower in the study 104. Upon request by CHMP, the MAH explained that these baseline levels were measured after the 4-week TEZ/IVA or IVA run-in period. After these 4 weeks an effect of TEZ/IVA was indeed expected, which explained that these lower SwCL levels seen in study 104 were 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. This was considered acceptable by CHMP.

Furthermore, some patients were included with baseline ppFEV$_1$ values below <40 and over 90. It is anticipated that the inclusion criterion pertaining to screening ppFEV$_1$ was met in all enrolled subjects in Study 104, but the ppFEV$_1$ 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 PI 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 was included in the study. The *S977F* mutations are also included in the EU Symkevi label, but not included in the study. This was 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 was unequal (e.g. over half of the IVA comparator group has the *G551D* mutation) is related to the prevalence of these mutations in the overall CF population. Thus, 14 RFs and 10 Gs mutations were recruited, and the MAH estimated that these 24 mutations covered the vast majority (> 95%) of patients with G and RF mutations. However, it should be noted that not all of these mutations were treated with ELX/TEZ/IVA in study 104; only 12 RFs, and 7 Gs mutations were 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 group in study 104, who then moved to ELX/TEZ/IVA in the open label study 110; this is further discussed below.

In the overall population, the use of concomitant medication was equal between the control group and the group receiving ELX/TEZ/IVA. In the F/RF (TEZ/IVA comparator group) and F/G (IVA comparator

group) populations the use of most concomitant medication was also in general well balanced. 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). Considering all other baseline parameters and concomitant medication are very balanced between the IVA and ELX/TEZ/IVA group it was considered unlikely that this imbalance was caused by a difference is CF severity between these groups. And, because of the large benefit seen with TEX/IVA/ELX, it was not expected that this slight imbalance would impact the B/R in the F/G CF patient population.

With regard to prior medication, it was considered of importance to know which percentage of the subjects received TEZ or TEZ/IVA prior to the study; as in the Kaftrio registration procedure, the $ppFEV_1$ 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 $ppFEV_1$ assessment. Therefore, and upon request by CHMP, the MAH performed subgroup analysis to compare treatment effect on $ppFEV_1$, 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 was well 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 3.7pp (95% CI: 2.8, 4.6; $p<0.0001$). As FEV_1 is linked to mortality, any significant difference could be considered clinically relevant. The result of the sensitivity analysis, a MMRM based on multiple imputations (MI), was consistent with the primary analysis. The 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; $p<0.0001$). Nevertheless, 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. This concern applies in particular to the F/RF group. To address this concern, 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 be considered to only provide 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 Kaftrio in combination with Kalydeco compared with the comparator group.

In order to establish the proportion of the treatment group that achieved a meaningful benefit in FEV_1, SwCl and CFQ-R RD score, responder analyses were performed using a threshold of 1.5 % and 2.5% for ppFEV1, <60 mmol/L and <30 mmol/L for SwCL and difference of 4 points in CFQ-R score. Analyses were performed for the total population and separately by comparator group. Overall, the

percentage of responders was higher in the ELX/TEZ/IVA group than in the control group, which confirms the benefit of ELX/TEZ/IVA. Consistent with the efficacy data seen so far, the effect in the F/RF patients is more moderate, but still present and considered clinically relevant.

For ppFEV1 and 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 showed consistent results with the main analyses for these endpoints.

A limitation of the current 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 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 was expected. Further, ELX/TEZ/IVA might also act via the non-*F508de*l allele. Therefore, a difference in effect size might be present between subjects with a gating or a residual function mutation. Therefore, upon request by CHMP, the MAH was requested to include 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 clinically relevant benefit. As ELX/TEZ/IVA is suggested to act trough the *F508del* allele, an effect over IVA was anticipated in this population. Within-group and between-group analyses for ppFEV1, SwCL and CFQ-R RD in the F/G population were provided by the MAH. Consistent with the within-group difference, 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: -25.5, -14.6; nominal p<0.0001) and in CFQ-RD of 8.9 points (95% CI: 3.8, 14.0; nominal p=0.0008). These results are overall considered clinically relevant and indicated that the ELX/TEZ/IVA had 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 *F508del* allele) put forward by the MAH. The cumulative effect of the 3 agents in F/G patients was very similar to what was achieved in F/MF CF patients.

F/RF population

Based on the MAH's *F508del* hypothesis, ELX/TEZ/IVA was expected to generate a positive clinical outcome in the F/RF population. 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 (-28.4, -21.2; nominal p<0.0001) and in CFQ-RD of 8.5 points (4.0, 13.1; nominal p=0.0003). The magnitude of effects in patients with F/RF on SwCl and CFQ-R with ELX/TEZ/IVA are 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 thus 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 have been be anticipated that treating an F/RF patient with ELX/TEZ/IVA might bring a total gain in ppFEV1 of approximately 14%. It would have been expected that the F/RF patients should have gained more in $ppFEV_1$ than the F/G patients, however, the F/G patients seem to have gained a better response. 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.

A similar pattern was also noted in the real-world US registry data, where F/G patients also seemed to obtain a better response to the triple combination versus F/RF patients. While it is agreed that a gain

of 2% over TEZ/IVA might be considered clinically relevant for a patient with an F/RF genotype, it was not certain that all F/RF patients will have achieved a clinically meaningful response.

The reason why F/RF subjects had lower $ppFEV_1$ improvements on ELX/TEZ/IVA compared to F/MF, F/F, and F/G subjects is unclear, but may be related to reduced severity of CF in those patients. F/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 F/MF mutations, the *F508del* mutation, and the *G551D* mutation, respectively. As a result, untreated patients with F/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 $ppFEV_1$.

Nevertheless, overall, the totality of the data supported the conclusions of an effect, with a 95% CI between 0.5 and 3.4 percentage points. Although, an MCID for FEV_1 cannot be defined, according to the "report of the workshop on endpoints for cystic fibrosis clinical trials", a treatment effect equivalent to the average annual loss in FEV_1 can be considered as clinically relevant. Based on published literature, the annual rate of $ppFEV_1$ decline in F/RF patients is around 0.70. When excluding *R117H* patients from the cohort, the annual decline is -1.05 points. Considering these annual decline rates, the 2.0 percentage point is considered clinically relevant. Furthermore, highly clinically relevant improvements in SwCL and CFQ-R are seen which further support the approval 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 $ppFEV_1$ 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 $ppFEV_1$ was 2.1 percentage points, and for CFQ-R it was 1.4 points increase.

Therefore, the efficacy outcomes for ELX/TEZ/IVA showed a clinically relevant improvement over the approved control therapy IVA or TEZ/IVA in the F/G and F/RF populations, respectively.

To further confirm the effects seen in the total and comparator group population, several additional analyses were provided, such as 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. In general, all these additional analyses resulted in consistent outcomes compared to the previous analysis presented. These analyses were considered to further confirm the beneficial effects of TEZ/IVA/ELX seen in study 104 in both the F/G and F/RF populations. These are discussed below.

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 analyses were performed by the MAH upon request by CHMP. Due to the COVID-19 pandemic, additional sensitivity analyses were done for pooled clinic and home assessment of the $ppFEV_1$ and or clinic only CFQ-R scores. The MAH provided these analyses also for the subgroups by the comparator. For the F/G group, LS mean difference in $ppFEV_1$ was 5.8% in the original and 5.9% in the sensitivity analysis. With regard to CFQ-R an LS mean difference of 8.9 points in the original and 8.3 points in the sensitivity analysis. For the F/RF group, the LS mean difference in ppFEV was 2.0% in the original and 1.8% in the sensitivity analysis. With regard to CFQ-R the LS mean difference of 8.5 points in the original and 9.1 points in the sensitivity analysis. Results per comparator subgroup were consistent with the original subgroup analysis.

Furthermore, the MAH also performed the subgroup analyses for age, sex, baseline lung function, and geographic region per comparator subgroup which were consistent with the overall results per comparator group.

In addition, the MAH was requested to perform 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. Overall, a beneficial effect was 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) seemed to be less pronounced in the patients who were already treated with a 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 suggested 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, hampered 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 were considered clinically relevant. Therefore, these results were not considered to further influence the B/R assessment.

Furthermore, per comparator subgroup, responder analyses were performed. Substantial increases in proportion of $ppFEV_1$, 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.

Elderly

Although the preliminary data from ongoing Study 110 in patients ≥65 years are limited, and the data provided an idea on the benefit in these older patients. Nevertheless, the numbers remain insufficient to determine whether response in these patients is different from younger adults. This has been adequately reflected in section 5.2 of the SmPC.

Supportive Efficacy data (Study 110)

With regard to data obtained from follow-up study 110, patients treated with control in study 104 and who then switched to Kaftrio had improvements in $ppFEV_1$, SwCl, and CFQ-R that were 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, this analysis is considered to be supportive of the results of study 104. The data also suggested that the gains in the Kaftrio treated group (in combination with Kalydeco) of study 104 were maintained in study 110.

Real world clinical data

Updated registry data were presented for patients with F/G and F/RF genotypes. $ppFEV_1$ 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. The newly provided RWE analysis further confirmed the beneficial effects of TEZ/IVA/ELX seen in study 104.

To identify the robustness of this effect and see whether different gating and residual function mutations might influence the effect size, it was of interest to see the clinical benefit in a subset based on specific mutations. In study 104, patients representing a total of 24 mutations (F/RF and F/G) were recruited, 12 F/RFs and 7 F/Gs were represented (with at least one patient) in the Kaftrio treatment group; the remaining 5 were treated with appropriate control. Moreover, information on additional

mutations were also provided from study 110 and from the real-world effectiveness registry data. For almost all of the genotypes included in both the F/G and F/RF categories, a clinical benefit of some degree could be seen, and in most cases, were considered to be 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 Kalydeco in combination with Kaftrio provides efficacy in patients with at least one F508del mutation.

Indication

Kalydeco is currently approved in combination with Kaftrio 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 considered the broad indication approvable:

Kalydeco tablets are indicated in a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1).

2.4.4. Conclusions on the clinical efficacy

A clinically relevant improvement in $ppFEV_1$, SwCL, and CFQ-R RD score over the approved control therapy IVA or TEZ/IVA in the F/G and F/RF population, respectively was shown in study 104.

Based on these results, the added benefit of the triple combination over approved therapies was determined, confirming that the ELX/TEZ/IVA is mainly acting through the *F508del* allele.

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 could be sufficient to conclude on the benefit of ELX/TEZ/IVA in the entire CF population with at least one F508del allele.

Therefore, the final indication granted by CHMP is as follows:

Kalydeco tablets are indicated in a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1).

Changes have been implemented in section 5.1 of the SmPC of Kalydeco to reflect the availability of results for the use of Kalydeco in combination with Kaftrio.

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 MAA (EMEA/H/C/005269/0000), 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 31).

Table 31 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.

Subject disposition data, demographic and other baseline characteristics, concomitant medications, and medical history are provided in the efficacy section.

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. 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 32 presents an overview of AEs.

Table 32 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.

Treatment-emergent AEs

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

Table 33 AEs Occurring in ≥5% of Subjects in Either 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.

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. Related AEs are presented in Table 34.

Table 34 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 1 subject. Severe AEs are presented by SOC and PT in Table 35.

Table 35 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 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 36 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, 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.

Pregnancy

One subject had a positive serum pregnancy test during the TE Period. This subject was in the control (TEZ/IVA) group and had a positive pregnancy test on Day 28 of the Treatment Period (ETT Visit). The subject discontinued treatment and the study.

Serious adverse event/deaths/other significant events

There were no deaths reported.

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 37 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 38 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. 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. None of these AEs was serious or led to treatment discontinuation or interruption.

Table 39 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.

Liver Function Tests (LFT)

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 40). 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 40 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)
ALP (U/L)		
Total, N1	123	126
>ULN to ≤1.5 × ULN	1 (0.8)	5 (4.0)
>1.5 to ≤2.5 × ULN	1 (0.8)	0
>2.5 to ≤5 × ULN	0	0
>5 to ≤20 × ULN	0	0
>20 × ULN	0	0

(ALT or AST) and total bilirubin		
Total, N1	123	125
(ALT >3 × ULN or AST >3 × ULN) and total bilirubin >2 × ULN	0	0
GGT (U/L)		
Total, N1	123	126
>ULN to ≤2.5 × ULN	6 (4.9)	9 (7.1)
>2.5 to ≤5 × ULN	0	1 (0.8)
>5 to ≤20 × ULN	0	1 (0.8)
>20 × 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.

Creatinine kinase (CK)

The majority of subjects had CK levels that remained within the normal range. However, mean CK levels in the ELX/TEZ/IVA group increased during the TE Period. The largest mean (SD) change from baseline was 74.6 (578.8) U/L at Day 15. Two (1.5%) subjects in the ELX/TEZ/IVA group had CK >5 × ULN, including 1 (0.8%) subjects with CK >10 × ULN. Both were considered possibly related. No subjects in the control group had CK >5 × ULN. Two (1.5%) subjects in the ELX/TEZ/IVA group had an AE of blood creatinine phosphokinase increased. Neither AE was serious or resulted in ELX/TEZ/IVA treatment discontinuation or interruption. No subjects in the control group had AEs of blood creatinine phosphokinase increased. No subject had AEs of rhabdomyolysis.

Vital Signs and ECGs

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 ECG parameters.

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

Ophthalmological examinations

While 24 patients (< 18 years) had a baseline eye examination at screening due to their age and due to the IVA component of treatment, no subjects had a post baseline exam in the TE period. 3 subjects in the ELX/TEZ/IVA group had a background history of a cataract, and one in the control group has a background history of a cortical cataract. There were no AEs relating to cataracts in Study 104.

Safety in special populations

Adolescents

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 (**Error! Reference source not found.**)).

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 (PT;). 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

No specific information has been provided. 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 (

). 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 41 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 in combination with Kalydeco, representing more than 5,800 patient-years.

2.5.1. Discussion on clinical safety

Patient population and exposure

The safety of Kalydeco in combination use with Kaftrio has been evaluated in 4 studies in CF patients aged 12 years and older, including a long-term extension study during the initial MAA for Kaftrio. In the current extension of indication application, 132 patients received Kalydeco in combination with Kaftrio in study 104, with mean and median exposure of 8 weeks indicating that the vast majority of the patients finalised the study treatment.

Adverse events, serious adverse events and deaths

There were 88 (66.7%) subjects in the ELX/TEZ/IVA group and 83 (65.9%) subjects in the control group with at least 1 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. While 5 subjects are listed as having interrupted ELX/TEZ/IVA due to an AE, an additional subject had an interruption of ELX/TEZ/IVA of 3 days due to a QT prolongation. The QTc value of 440msec was not considered significant compared to the patient's baseline ECG and was also less than 500msec. Furthermore, the patient resumed treatment after 3 days with no further QTc increases. This QT prolongation was thus not considered as an AE. In addition, an event of pregnancy was reported in Study 104.

There were no AEs relating to cataracts in Study 104.

Related SAEs were observed only in 2 subjects in the control group. They were anxiety, depression, and haemoptysis. The safety appears similar to the safety established in the clinical development program in the initial ELX/TEZ/IVA MAA.

In the case of the treatment group, none of the SAEs were considered to be related. The 6 SAEs in those 5 subjects that were in the treatment group were all considered unrelated and included: infective pulmonary exacerbations of CF, cellulitis, tinnitus, cholecystitis and haemoptysis.

Adverse events of special interest

-Elevated Transaminase Events

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.

In Study 104, there was a higher incidence of elevated transaminase AEs in the ELX/TEZ/IVA group than in the placebo group. However, 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 further changes are deemed necessary.

-Rash events

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. All rash events in the ELX/TEZ/IVA group were mild or moderate in severity. Rash is a known AE of ELX/TEZ/IVA. There are no new insights in this AESI. Rash is already addressed in the SmPC and RMP; no further changes are deemed necessary.

-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. Susceptibility for influenza virus infections is also an important identified risk within the RMP. In Study 104, there were only 4 cases of influenza, 2 each for both the treatment groups. Influenza appears to have been less frequent in Study 104 without a difference between the treatment groups.

Laboratory findings

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. Furthermore, CK elevations are listed as an ADRs in section 4.8 of the SmPC, thus, no further actions were deemed necessary.

Rises in blood bilirubin were seen in a small number of patients (4 subjects) in the ELX/TEZ/IVA group in Study 104. No AEs related to increased bilirubin were serious or resulted in ELX/TEZ/IVA discontinuation. One (0.8%) subject had AEs of conjugated bilirubin increased and blood bilirubin increased that resulted in ELX/TEZ/IVA interruption. Similar findings of bilirubin rises were seen Study 102. The rises in bilirubin seen in Study 104 appear consistent with those seen in Study 102; no further actions were deemed necessary.

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. Blood pressure increase is a listed ADR in section 4.8 of the SmPC, thus, no further actions were deemed as necessary.

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

The safety results appeared generally consistent with the known safety profile; no new safety concerns were identified on the provided data. Furthermore, an update of SmPC section 4.8 was not deemed necessary as the frequencies of the ADRs in study 104 were not higher than the frequencies of the ADRs in pivotal study 102 in F/MF patients or in the cumulative database of studies 102 and 104.

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.

Assessment of paediatric data on clinical safety

A total of 24 adolescents were enrolled in study 104, 9 subjects were enrolled in the control group and 15 in the ELX/TEZ/IVA group. No subjects in the ELX/TEZ/IVA group had serious AEs (SAEs), severe AEs, or AEs that led to study drug discontinuation. Overall, the AEs were consistent with the overall study population.

2.5.2. Conclusions on clinical safety

Kaftrio in combination use with Kalydeco was generally safe and well-tolerated for 8 weeks.

Overall, safety data from Study 104 are consistent with the established safety profile of Kalydeco in combination use with Kaftrio. No significant 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. Nevertheless, the MAH confirmed that F/G and F/RF genotypes will be included in the planned post-authorisation safety study (PASS, category 3) consistent with the applied indication of the treatment of patients with CF aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene, regardless of the second allele (F/any). This will allow to gather additional long-term safety data post-approval.

Furthermore, the safety of Kalydeco in combination with Kaftrio will be further monitored in the PSURs in the post-marketing setting.

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 11.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 11.0 with the following content:

Safety concerns

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

The important potential risk of "Concomitant use of IVA with strong CYP3A inhibitors or inducers" was removed given that there are no additional pharmacovigilance or risk minimisation activities associated with this potential risk.

Pharmacovigilance plan

No changes to the pharmacovigilance plan were implemented.

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
Study 126 Ongoing	<u>IVA Arm</u> In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation: • To evaluate the safety of long-term IVA treatment • To evaluate the PD of long-term IVA treatment • To evaluate the efficacy of long-term IVA treatment <u>Observational Arm</u> To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation	• Hepatotoxicity • Cataract • Indicated use in children aged <24 months old at initiation	Final Report	March 2022
Study 122 Ongoing	• To confirm the long-term safety and effectiveness of Kalydeco (IVA) in US CF patients with the *R117H-CFTR* mutation <18 years of age • To describe the long-term safety and effectiveness of Kalydeco in CF patients with the *R117H-CFTR* mutation overall and in patients ≥18 years of age	• Indicated use in children aged <6 years (with the *R117H* mutation)	Final Report	December 2020

CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; IVA: ivacaftor; MA: market authorisation; PD: pharmacodynamics; PV: pharmacovigilance; US: United States

Note: Studies 126 and 122 address a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

Risk minimisation measures

The risk minimisation measures in relation to "Concomitant use of IVA with strong CYP3A inhibitors or inducers" were removed accordingly.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up form **Additional PV activities:** None
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 Prescription only **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** Study 126 Study 122

PL: Patient Leaflet; SmPC: Summary of Product Characteristics

Note: Studies 126 and 122 address a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 5.1 and 5.2 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

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

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.

3.1.2. Available therapies and unmet medical need

Two broad types of CF therapies are authorised: symptomatic therapy and CFTR modulator therapy. 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 elexecaftor), 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 is as follows:

Kalydeco tablets are indicated in a combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene.

This proposed indication covers the F/F genotypes and F/MF 'minimal function' genotypes in which Kalydeco is already approved in combination with Kaftrio. 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 Kalydeco in combination with Kaftrio was presented in the initial Marketing Authorisation Application, for heterozygous patients with minimal function mutations in study 102 (F/MF) and for homozygous patients in study 103 (F/F); and the follow-up study 105. The main evidence for the extension of the indication to a broad population of CF patients with at least one F508del allele is obtained from one clinical trial, study 104, where heterozygous patients with additional type of mutations are studies i.e. patients with gating mutations (F/G) and patients with residual function mutations (F/RF).

Study 104 in CF patients 12 years and older is an 8-week, randomised, double-blind, controlled study in subjects heterozygous for the *F508del* mutation and a gating or residual function mutation (F/G and

F/RF genotypes respectively). 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 though in the ELX/TEZ/IVA group (within-group change).

Percent predicted FEV1 as a surrogate endpoint is well-established, and an improvement over time in this endpoint is related to improved lung function as lung disease is one of the main drivers of morbi-mortality in patients with CF. Pulmonary exacerbations have also 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 one of the main goals of treatment of CF.

3.2. Favourable effects

CF patients included in study 104 (both F/G and RF)

In study 104, the mean absolute within-group change in ppFEV1 from baseline through week 8 in the ELX/IVA/TEZ group was 3.7 pp (95% CI: 2.8, 4.6; p<0.0001). The 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 pp; 95% CI: 2.2, 4.7; p<0.0001).

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

For the respiratory domain (RD) score of CFQ-R, the within-group difference was an increase in score of 10.3 points (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 (5.3, 12.1; nominal p<0.0001).

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.

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 difference showed a beneficial change of ELX/TEZ/IVA treatment in ppFEV1 of 5.8 percentage points (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 difference showed a beneficial change of ELX/TEZ/IVA treatment in ppFEV1 of 2.0 percentage points (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 (4.0, 13.1; nominal p=0.0003) compared to TEZ/IVA combination therapy.

Several additional analyses were provided, being 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 F/RF)

The study was not powered for between-group comparisons, but a formal between-group comparison was 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. Long-term efficacy data are provided based on the supportive study 110 but remain overall 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. 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 increase 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 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 IA data (both F/F and F/MF) which were provided in the initial submission (271 subjects had an exposure of ≥48 weeks); these 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 (category 3) 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 subgroup 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 42 Effects Table for Kalydeco tablets for the treatment of adult and adolescent patients with cystic fibrosis who have who have at least one *F508del* mutation in the *CFTR* gene (database lock: 30 June 2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ppFEV1	Change 0-8 weeks LSM (95% CI)	pp	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

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
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 is based on the hypothesis that Kaftrio in combination with Kalydeco mainly acts though the *F508del* allele and that all patients with an *F508del* allele could be included in the indication. During the assessment of the Kaftrio initial marketing authorisation application, the effects in the F/MF population and all additionally provided information made it reasonable, 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. Therefore, a study in F/RF or F/G patients was required to determine the added benefit of the triple combination in combination with IVA over approved IVA and TEZ/IVA and to further assess the above-mentioned hypothesis. Clinical data from study 104 are provided to support this application in the F/G and F/RF CF 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. This would mean that efficacy for non-tested populations of F/MF, F/RF and F/G should in principle 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 treatment 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 determine 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.

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 Kaftrio initial MAA.

Safety

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

The safety results appeared 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 number of the new safety set is relatively small. The planned PASS, which will also include patients with F/RF and F/G mutations, is expected to provide further safety data in the broad indication.

3.7.2. Balance of benefits and risks

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. The 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. These results can be regarded as clinically relevant.

To identify the robustness of the effect and see whether different gating and residual function mutations might influence the effect size, it was of interest to see the clinical benefit in a subset based on specific mutations. In study 104, patients representing a total of 24 mutations (F/RF and F/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, a 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 Kalydeco in combination with Kaftrio provides efficacy in patients with at least one *F508del* mutation.

Overall the safety profile is consistent with that seen in F/F and F/MF patients, and therefore acceptable in F/F and F/RF patients.

Kalydeco is currently approved in combination with Kaftrio 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 considered the broad indication approvable:

Kalydeco tablets are indicated in a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Kalydeco 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 for Kalydeco (ivacaftor) tablets in combination regimen with Kaftrio (ivacaftor/tezacaftor/elexacaftor) tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) 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). As a consequence, sections 4.1, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to Version 11.0. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes 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 P/0163/2020 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 Kalydeco is not similar to TOBI Podhaler, Bronchitol, Symkevi and Kaftrio within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

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 'Kalydeco EMEA/H/C/002494/II/0089'

[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