12 October 2023
EMA/297123/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kaftrio

Ivacaftor / Tezacaftor / Elexacaftor

Procedure no: EMEA/H/C/005269/P46/011

Note

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

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

Table of contents

1. Introduction

On 02 May 2023, the MAH submitted a completed paediatric study for Cystic Fibrosis patients 12 years of age and older, heterozygous for *F508del* and a gating or residual function mutation, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene. CTFR is a channel that regulates the flow of chloride and other anions across epithelia in multiple organs and tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands. Despite progress in the treatment of CF with antibiotics and mucolytics, the current median age at death among people with CF is approximately 30 years, and the predicted median age of survival is approximately 47 years.

The most common disease-causing mutation is *F508del*: approximately 84.7% of people with CF in the US and 81.1% in Europe have at least one *F508del* allele. At present, there is no cure for CF. CFTR modulators (CFTRm; i.e., correctors and potentiators) represent a major advancement in the treatment of CF because they are systemic therapies that target the underlying cause of the disease and have been shown to improve CF survival by modifying the course of disease. Approved treatment regimens include ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA dual combination therapy (Orkambi™), tezacaftor (TEZ)/IVA dual combination therapy (Symdeko™, Symkevi™) and elexacaftor (ELX)/TEZ/IVA triple combination therapy (TrikaftaTM, KaftrioTM).

The elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) regimen previously demonstrated clinical benefit in patients with a single *F508del* allele, regardless of the mutation of the second allele. A pivotal Phase 3 program in subjects with CF 12 years of age or older demonstrated that ELX/TEZ/IVA provides substantial improvements in lung function, CFTR function, and nutritional status, and was generally safe and well tolerated with a low rate of treatment discontinuation.

Kaftrio obtained a marketing authorization in August 2020 and is currently indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Table 1: Dosing recommendation for patients aged 6 years and older

Age	Morning dose	Evening dose
6 to <12 years weighing <30 kg	Two tablets, each containing ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg	One tablet containing ivacaftor 75 mg
6 to <12 years weighing ≥30 kg	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg
≥12 years	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg

The MAH now submitted the results of Study VX18-445-110 ("Study 110") as per requirement of Article 46 of the "Paediatric Regulation" (EC) 1901/2006. Study 110 is a Phase 3, multicenter, open-label study (OLS) in subjects with CF 12 years of age and older, heterozygous for *F508del* and a gating or residual function mutation (F/G and F/RF genotypes), who completed Study VX18-445-104 (Study 104). The primary objective was to evaluate the long-term safety and tolerability of ELX/TEZ/IVA.

The MAH stated that Study VX18-445-110 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The following tablets were used in the study:

- ELX/TEZ/IVA 100-mg/50-mg/75-mg fixed-dose combination (FDC) tablet
- IVA 150-mg tablet

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study VX18-445-110, a Phase 3, multicenter, open-label study (OLS) in subjects with CF 12 years of age and older, heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes), who completed Study VX18-445-104 (Study 104).

2.3.2. Clinical study

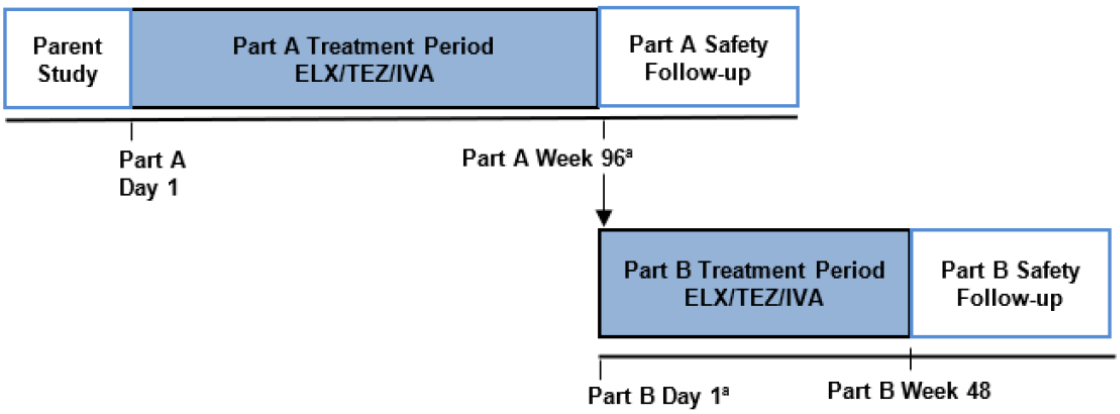
Study VX18-445-110

Description

Study VX18-445-110 was a Phase 3, 2-part, multicenter, OLS for subjects who completed the last Treatment Period visit in the parent study (Study 104) and met eligibility criteria (Figure 1). Subjects in certain countries who completed Part A had the opportunity to participate in Part B.

The total study duration was up to approximately 148 weeks (from the first dose of study drug in this study), including a Treatment Period of up to 144 weeks (96 weeks in Part A and 48 weeks in Part B [in certain countries]) and a 4-week Safety Follow-up Period.

The study period was from 05 December 2019 until 16 December 2022.



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: Parent study refers to Study 104. Note that the figure is not drawn to scale.
a Subjects whose Part B Day 1 was on the same day or within 1 calendar day as the Part A Week 96 Visit did NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 was more than 1 calendar day after Part A Week 96 Visit completed all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

Figure 1 Study design

CHMP comment

Part B was added at the time of version 1.2 of the Clinical Study Protocol (14 May 2021) for all countries except NL, and version 1.3 (21 December 2021) for NL (see Conduct of Study below). However, according to the clinical overview submitted by the Applicant, patients in only certain countries were offered Part B of this study (those seem to be AU, BE, FR, IT, ES, and NL). It is not completely understood why Part B was only accessible for subjects in these countries. However, considering the sufficiently long treatment period of Part A, the fact that only safety was assessed in Part B, and most patients discontinued Part B due to commercial availability of Kaftrio, this issue is not further pursued.

Methods

Study participants

The study included male and female CF subjects 12 years of age or older with F/G or F/RF genotypes.

Key eligibility criteria are shown in Table 1.

Table 1 Key eligibility criteria in Study 110

Inclusion Criteria	Exclusion Criteria

• Current participation in Study 104, which was defined as 1 of the following:
  ○ On study drug treatment in Study 104 as of the day prior to the Day 1 Visit in this study
  ○ On study drug interruption in Study 104 as of the day prior to the Day 1 Visit in this study
• Subjects who permanently discontinued ELX/TEZ/IVA in Study 104 for any reason other than enrolling into this study were not eligible
• Willing to remain on a stable CF regimen through completion of study participation
	• History of any illness or any clinical condition that could confound the results of the study or pose an additional risk in administering study drug to the subject
	• Pregnant and breast-feeding females
	• History of drug intolerance in Study 104 that would pose an additional risk to the subject
	• Current participation in an investigational drug study

Sources: Study 110 Protocol/Sections 8.1 and 8.2
CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

CHMP comment

Key inclusion criteria of Study 104 were age 12 years and older, FEV1 value ≥40% and ≤90% of predicted, confirmed CF diagnosis, stable CF disease, and heterozygous for *F508del* and either a gating or residual function mutation (F/G or R/RF genotype). These inclusion criteria were previously considered acceptable. The additional exclusion criteria are also acceptable.

Treatments

All subjects received two FDC tables of ELX/TEZ/IVA in the morning and one IVA tablet in the evening (Table 2). This is the same dosage as that evaluated in the parent study, Study 104.

Table 2 Dosages

ELX Dosage	TEZ Dosage	IVA Dosage
200 mg qd	100 mg qd	150 mg q12h

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

ELX/TEZ/IVA was administered for approximately 96 weeks in Part A and up to approximately 48 weeks in Part B.

CHMP comment

The used dosing is in line with the parent study and the approved posology. The 96- or 144-week treatment period meets the safety assessment criteria of the EMA guideline on CF (CHMP/EWP/9147/08).

Objective(s)

Primary objective:
To evaluate the long-term safety and tolerability of ELX/TEZ/IVA in subjects with CF who are heterozygous for the *F508del* mutation and a gating (F/G) or residual function (F/RF) mutation.

Secondary Objectives:
• To evaluate the long-term efficacy of ELX/TEZ/IVA
• To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA

Outcomes/endpoints

Primary endpoint:
Safety and tolerability of long-term treatment with ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry.

Secondary endpoints:

- Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1)
- Absolute change in sweat chloride (SwCl)
- Absolute change in body mass index (BMI)
- Absolute change in BMI z-score
- Absolute change in body weight
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score.

Sample size

The primary and secondary objectives of the study are the evaluation of the long-term safety and tolerability, and long-term efficacy of ELX/TEZ/IVA. This is an open-label study that will enrol subjects who complete the last Treatment Period visit in the parent study and meet eligibility criteria. The parent study is a Phase 3 Vertex study investigating ELX/TEZ/IVA (Study 104).

Approximately 250 subjects were planned to be enrolled.

CHMP comment

The primary endpoint of safety and tolerability after long-term treatment is appropriate for an open-label extension study. Secondary endpoints are in line with commonly used efficacy endpoints.

A sample size of 250 subjects for Part A is also considered acceptable. In the end, 251 patients were included. It appears that no sample size intention was set for Part B, which is acceptable considering the sufficiently long treatment period of Part A to assess long-term safety and tolerability.

Randomisation and blinding (masking)

N/A

Statistical Methods

Analysis sets

The following analysis sets were defined:

- **Open-label (OL) All Subjects Set**: all subjects who were enrolled (defined as subject having data in the clinical database) in the OLS.
- **OL Full Analysis Set (OL-FAS)**: all enrolled subjects who have received at least 1 dose of study drug in the open-label study.
- **OL Safety Set (OL-SS)**: all subjects who received at least 1 dose of study drug in the OLS.

Efficacy analyses

The parent study baseline is used to calculate the change from baseline for continuous efficacy endpoints unless otherwise specified. Data of continuous endpoints at visits in the parent study are analysed using the same mixed-effects model for repeated measures (MMRM) approach as described in the SAP for the parent study. The resulting estimates will be identical to what is in the CSR of the parent study. Similarly, data of continuous endpoints at visits in the OL efficacy period for Part A are analysed using a separate MMRM. The results obtained from the parent study and OLE efficacy period will be displayed one followed by the other.

The focus of the efficacy analysis is to characterise the long-term treatment effects using change from baseline for each treatment group in the parent study. P values were not planned to be presented.

Efficacy analysis is only applicable to Part A.

Safety analyses

The primary objective of the study was the evaluation of long-term safety and tolerability of the triple combination. All safety analyses for Part A and B are based on the treatment-emergent (TE) Period (i.e., time from first dose of Study 110 to 28 days after last dose or completion date of study participation) in the OL-SS. The overall long-term safety profile of study drug is assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values
- ECGs
- Vital signs
- Pulse oximetry

The triple combination safety baseline was planned to be used to calculate the change from baseline for continuous safety endpoints. The TC safety baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study (if the subject actually received at least one dose of ELX/TEZ/IVA) or the first dose in the OLS.

Only descriptive analysis of safety and no statistical testing was planned to be performed.

Multiplicity control

Not applicable as no hypothesis test is planned for safety analysis, unless specified otherwise.

Interim analyses

Interim analyses (IAs) may take place at any time during the study at the discretion of the sponsor. In the event that the parent study is still ongoing, a limited Vertex team may be unblinded to the treatment assignments in the parent study for the purpose of reviewing the interim results, and will

not be involved in or influence the conduct of the remaining part of the parent study to protect the integrity of the parent study.

CHMP comment

Statistical methods are agreed for this open-label extension study.

Results

Participant flow

Of the 251 subjects who received at least 1 dose of study drug in **Part A**, 217 (86.5%) subjects completed study drug treatment and 215 (85.7%) subjects completed the study. A total of 84 (33.5%) subjects rolled over into Part B.

Of the 84 subjects who received at least 1 dose of study drug in **Part B**, 1 (1.2%) subject completed study drug treatment and the study; 81 (96.4%) subjects discontinued treatment and the study due to commercial drug availability.

Table 3 Subject Disposition (OL All Subjects Set for Part A)

Disposition Reason	Control in Study 104 n (%)	ELX/TEZ/IVA in Study 104 n (%)	Any ELX/TEZ/IVA n (%)
OL All Subjects Set for Part A	121	130	251
OL Full Analysis Set for Part A	121	130	251
OL Safety Set for Part A	121	130	251
Completed treatment	98 (81.0)	119 (91.5)	217 (86.5)
Prematurely discontinued treatment	23 (19.0)	11 (8.5)	34 (13.5)
Reason for discontinuation of treatment			
AE	6 (5.0)	8 (6.2)	14 (5.6)
Subject refused further dosing (not due to AE)	6 (5.0)	1 (0.8)	7 (2.8)
Commercial drug is available for subject	4 (3.3)	0	4 (1.6)
Death	1 (0.8)	0	1 (0.4)
Non-compliance with study drug	1 (0.8)	0	1 (0.4)
Other non-compliance	0	1 (0.8)	1 (0.4)
Pregnancy (self or partner)	4 (3.3)	0	4 (1.6)
Other	1 (0.8)	1 (0.8)	2 (0.8)
Completed study	96 (79.3)	119 (91.5)	215 (85.7)
Prematurely discontinued the study	25 (20.7)	11 (8.5)	36 (14.3)
Reason for discontinuation from study			
AE	6 (5.0)	8 (6.2)	14 (5.6)
Withdrawal of consent (not due to AE)	6 (5.0)	1 (0.8)	7 (2.8)
Commercial drug is available for subject	6 (5.0)	0	6 (2.4)
Death	1 (0.8)	0	1 (0.4)
Other non-compliance	1 (0.8)	1 (0.8)	2 (0.8)
Other	5 (4.1)	1 (0.8)	6 (2.4)
Rollover to Part B	38 (31.4)	46 (35.4)	84 (33.5)

Source: Table 14.1.1

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; OL: open-label; OLS: open-label study; TEZ: tezacaftor

Notes: OL All Subjects Set for Part A was defined as all subjects who were enrolled (defined as subject having data in the clinical database for the OLS) in the OLS Part A. OL Full Analysis Set for Part A was defined as all enrolled subjects who received at least 1 dose of study drug in the OLS Part A (treatment label is based on the treatment that the subjects were assigned to in the parent study). OL Safety Set for Part A was defined as all subjects who received at least 1 dose of study drug in the OLS Part A. Subjects were assigned based on parent study actual treatment. Percentages are based on the number of subjects in the OL Full Analysis Set for Part A.

Table 4 Subject Disposition (OL All Subjects Set for Part B)

Disposition Reason	Control in Study 104 n (%)	ELX/TEZ/IVA in Study 104 n (%)	Any ELX/TEZ/IVA n (%)
OL All Subjects Set for Part B	38	46	84
OL Full Analysis Set for Part B	38	46	84
OL Safety Set for Part B	38	46	84
Completed treatment	1 (2.6)	0	1 (1.2)
Prematurely discontinued treatment	37 (97.4)	46 (100.0)	83 (98.8)
Reason for discontinuation of treatment			
Subject refused further dosing (not due to AE)	1 (2.6)	0	1 (1.2)
Commercial drug is available for subject	35 (92.1)	46 (100.0)	81 (96.4)
Physician decision	1 (2.6)	0	1 (1.2)
Completed study	1 (2.6)	0	1 (1.2)
Prematurely discontinued the study	37 (97.4)	46 (100.0)	83 (98.8)
Reason for discontinuation from study			
Withdrawal of consent (not due to AE)	1 (2.6)	0	1 (1.2)
Commercial drug is available for subject	35 (92.1)	46 (100.0)	81 (96.4)
Physician decision	1 (2.6)	0	1 (1.2)

Source: Table 14.1.1b

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; OL: open-label; OLS: open-label study; TEZ: tezacaftor

Notes: OL All Subjects Set for Part B was defined as all subjects who were enrolled (defined as subject having data in the clinical database for the OLS) in the OLS Part B. OL Full Analysis Set for Part B was defined as all enrolled subjects who received at least 1 dose of study drug in the OLS Part B (treatment label is based on the treatment that the subjects were assigned to in the parent study). OL Safety Set for Part B was defined as all subjects who received at least 1 dose of study drug in the OLS Part B. Subjects were assigned based on parent study actual treatment. Percentages are based on the number of subjects in the OL Full Analysis Set for Part B.

CHMP comment

In Part A, more patients from the control group of Study 104 prematurely discontinued the study compared to those who received treatment in Study 104 (20.7% vs 8.5%, respectively). Withdrawal of consent (not due to AE) and commercial drug available were the main reasons for this discrepancy.

In Part B, almost all patients discontinued prematurely due to availability of the commercial drug. As such, results for Part A are considered most important for this procedure.

Recruitment

The study was conducted at 92 study sites in the US, Canada, the EU, Australia and the UK.

Study initiation: 05 December 2019 (date first eligible subject signed the informed consent form)
Study completion: 16 December 2022 (date last subject completed the last visit)

Conduct of study

Country-specific amendments to the protocol were prepared for 7 countries (Table 5).

Table 5 Summary of Study 110 Protocol Changes

Protocol Version	Date	Key Changes
1.0	30 May 2019	Original Version
1.1UK	03 June 2019	Removed allowance for subjects who became eligible to receive commercially available TC to be discontinued from study drug dosing.
1.2AU/BE/FR/IT/ES	14 May 2021	• Extended the Treatment Period by an additional 48 weeks (Part B) to evaluate the safety of ELX/TEZ/IVA beyond 96 weeks of treatment • Revised the study design to provide the opportunity for subjects who depart this study to enroll in another qualified Vertex study of investigational CFTR modulators, but do not receive the first study drug dose in the Treatment Period of the other study, to return to this study • Removed language allowing Vertex to recommend discontinuation for subjects with relevant genotypes, as clinically meaningful benefit was demonstrated in the parent study. • Revised the statistical analysis section to reflect the updated study design. • Clarified language regarding height measurement and ophthalmological examination timings for Parts A and B.
1.3NL	21 December 2021	• Extended the Treatment Period by an additional 48 weeks (Part B) to evaluate the safety of ELX/TEZ/IVA beyond 96 weeks of treatment • Revised the study design to provide the opportunity for subjects who depart this study to enroll in another qualified Vertex study of investigational CFTR modulators, but do not receive the first study drug dose in the Treatment Period of the other study, to return to this study • Removed language allowing Vertex to recommend discontinuation for subjects with relevant genotypes, as clinically meaningful benefit was demonstrated in the parent study. • Revised the statistical analysis section to reflect the updated study design. • Clarified language regarding height measurement and ophthalmological examination timings for Parts A and B.

ELX: elexacaftor; IVA: ivacaftor; TC: triple combination; TEZ: tezacaftor

On 17 October 2022, the statistical analysis plan (SAP) was amended. Safety analyses for Part B were added to SAP version 2.0.

Vertex implemented safety measures to provide subjects the opportunity to continue participation in this study while ensuring their safety by minimizing the risk to coronavirus disease (COVID-19) exposure through travel. Implemented measures included, among others, shipment of study drug from site to subject's home, telephone/video call for safety assessments, in home assessments, and use of local laboratories.

Important protocol deviations (IPDs) were defined as any protocol deviation that may significantly affect the completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPDs were reported in 6 subjects in **Part A**, mainly pertaining to study conduct/procedures. None of these impacted subject safety or efficacy assessments. There were no IPDs in **Part B**.

Baseline data

Baseline demographics in Study 110 were the same as the parent study baseline demographics.

Table 6 Demographics at Parent Study Baseline (OL-FAS Part A)

	Control in 445-104 N = 121	ELX/TEZ/IVA in 445-104 N = 130	Any ELX/TEZ/IVA N = 251
Sex, n (%)			
Male	64 (52.9)	63 (48.5)	127 (50.6)
Female	57 (47.1)	67 (51.5)	124 (49.4)
Childbearing potential at parent study baseline, n (%)			
Yes	44 (77.2)	50 (74.6)	94 (75.8)
No	13 (22.8)	17 (25.4)	30 (24.2)
Age at parent study baseline (years)			
n	121	130	251
Mean (SD)	38.0 (14.2)	37.8 (14.6)	37.9 (14.4)
Median	37.9	37.2	37.6
Min, max	13.4, 72.7	12.3, 69.8	12.3, 72.7
Ethnicity, n (%)			
Hispanic or Latino	4 (3.3)	5 (3.8)	9 (3.6)
Not Hispanic or Latino	109 (90.1)	115 (88.5)	224 (89.2)
Not collected per local regulations	8 (6.6)	10 (7.7)	18 (7.2)
Race, n (%)			
White	106 (87.6)	120 (92.3)	226 (90.0)
Black or African American	2 (1.7)	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 (3.3)	1 (0.8)	5 (2.0)
Not collected per local regulations	9 (7.4)	9 (6.9)	18 (7.2)
Geographic Region, n (%)			
North America	45 (37.2)	48 (36.9)	93 (37.1)
Europe and Australia	76 (62.8)	82 (63.1)	158 (62.9)

- Percentages of childbearing women are based on the number of women in the OL FAS for Part A.
- 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.
- If a subject is reported to have multiple races, then the subject is counted for each race reported.

Table 7 Demographics at Parent Study Baseline (OL-FAS Part B)

	Control in 445-104 N = 38	ELX/TEZ/IVA in 445-104 N = 46	Any ELX/TEZ/IVA N = 84
Sex, n (%)			
Male	18 (47.4)	24 (52.2)	42 (50.0)
Female	20 (52.6)	22 (47.8)	42 (50.0)
Childbearing potential at parent study baseline, n (%)			
Yes	16 (80.0)	18 (81.8)	34 (81.0)
No	4 (20.0)	4 (18.2)	8 (19.0)
Age at parent study baseline (years)			
n	38	46	84
Mean (SD)	34.9 (12.3)	37.5 (15.8)	36.3 (14.3)
Median	32.5	37.2	34.5
Min, max	15.3, 60.4	12.3, 64.3	12.3, 64.3
Ethnicity, n (%)			
Hispanic or Latino	2 (5.3)	3 (6.5)	5 (6.0)
Not Hispanic or Latino	35 (92.1)	41 (89.1)	76 (90.5)
Not collected per local regulations	1 (2.6)	2 (4.3)	3 (3.6)
Race, n (%)			
White	30 (78.9)	42 (91.3)	72 (85.7)
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	3 (7.9)	1 (2.2)	4 (4.8)
Not collected per local regulations	5 (13.2)	3 (6.5)	8 (9.5)
Geographic Region, n (%)			
North America	0	0	0
Europe and Australia	38 (100.0)	46 (100.0)	84 (100.0)

- Percentages of childbearing women are based on the number of women in the OL FAS for Part B.
- 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.
- If a subject is reported to have multiple races, then the subject is counted for each race reported.

Table 8 Parent Study Baseline Disease Characteristics (OL-FAS Part A)

	Control in 445-104 N = 121	ELX/TEZ/IVA in 445-104 N = 130	Any ELX/TEZ/IVA N = 251
Weight (kg)			
n	121	130	251
Mean (SD)	69.1 (16.5)	69.6 (16.4)	69.4 (16.4)
Median	67.0	67.4	67.0
Min, max	41.0, 127.5	43.5, 125.2	41.0, 127.5
Height (cm)			
n	121	130	251
Mean (SD)	169.3 (9.4)	169.4 (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)			
n	121	130	251
Mean (SD)	23.91 (4.39)	24.10 (4.69)	24.01 (4.54)
Median	23.11	23.15	23.14
Min, max	16.51, 41.62	17.10, 44.36	16.51, 44.36
BMI z-score (subjects ≤20 years old at parent study baseline)			
n	12	17	29
Mean (SD)	-0.14 (0.80)	-0.01 (1.11)	-0.07 (0.98)
Median	-0.14	-0.15	-0.15
Min, max	-1.30, 1.28	-1.39, 2.20	-1.39, 2.20
Comparator group in parent study, n (%)			
TEZ/IVA	78 (64.5)	81 (62.3)	159 (63.3)
IVA	43 (35.5)	49 (37.7)	92 (36.7)

ppFEV$_1$ category at the Day -14 Visit in parent study[1], n (%)			
<70	66 (54.5)	74 (56.9)	140 (55.8)
≥70	55 (45.5)	56 (43.1)	111 (44.2)
ppFEV$_1$ category at parent study baseline, n (%)			
<40	2 (1.7)	2 (1.5)	4 (1.6)
≥40 to <70	62 (51.2)	70 (53.8)	132 (52.6)
≥70 to ≤90	50 (41.3)	51 (39.2)	101 (40.2)
>90	7 (5.8)	7 (5.4)	14 (5.6)
ppFEV$_1$ at parent study baseline			
n	121	130	251
Mean (SD)	67.7 (16.2)	67.0 (15.8)	67.3 (16.0)
Median	67.7	68.1	68.0
Min, max	31.1, 104.1	29.7, 113.5	29.7, 113.5
Sweat chloride (mmol/L) category at the Day -14 Visit in parent study[1], n (%)			
<30	22 (18.2)	23 (17.7)	45 (17.9)
≥30	99 (81.8)	107 (82.3)	206 (82.1)
Sweat chloride (mmol/L) at parent study baseline			
n	121	130	251
Mean (SD)	57.0 (25.4)	59.7 (27.0)	58.4 (26.2)
Median	54.0	56.8	56.5
Min, max	13.5, 109.5	10.0, 116.5	10.0, 116.5
CFQ-R respiratory domain score at parent study baseline			
n	121	130	251
Mean (SD)	77.2 (15.9)	76.7 (16.6)	77.0 (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*, n (%)			
Yes	65 (53.7)	69 (53.1)	134 (53.4)
No	56 (46.3)	61 (46.9)	117 (46.6)
Prior use of azithromycin*, n (%)			
Yes	55 (45.5)	58 (44.6)	113 (45.0)
No	66 (54.5)	72 (55.4)	138 (55.0)
Prior use of inhaled antibiotic*, n (%)			
Yes	54 (44.6)	50 (38.5)	104 (41.4)
No	67 (55.4)	80 (61.5)	147 (58.6)
Prior use of any bronchodilator*, n (%)			
Yes	106 (87.6)	112 (86.2)	218 (86.9)
No	15 (12.4)	18 (13.8)	33 (13.1)
Prior use of any inhaled bronchodilator*, n (%)			
Yes	106 (87.6)	112 (86.2)	218 (86.9)
No	15 (12.4)	18 (13.8)	33 (13.1)
Prior use of any inhaled hypertonic saline*, n (%)			
Yes	54 (44.6)	59 (45.4)	113 (45.0)
No	67 (55.4)	71 (54.6)	138 (55.0)
Infection with *Pseudomonas aeruginosa* within 2 years prior to screening (parent study), n (%)			
Positive	73 (60.3)	79 (60.8)	152 (60.6)
Negative	48 (39.7)	51 (39.2)	99 (39.4)

- 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.
- [1]: If the Day -14 value is not valid or not available, the most recent available value is used.
- *: For subjects who actually received ELX/TEZ/IVA in the parent study, prior medication use refers to medication taken during 56 days before the first dose date of study drug in the parent study Treatment Period or medication taken during the Run-in Period. For subjects who did not receive ELX/TEZ/IVA in the parent study, prior medication use refers to medication taken during 56 days before the first dose date of study drug in the OLS.

Table 9 Parent Study Baseline Disease Characteristics (OL-FAS Part B)

	Control in 445-104 N = 38	ELX/TEZ/IVA in 445-104 N = 46	Any ELX/TEZ/IVA N = 84
Weight (kg)			
n	38	46	84
Mean (SD)	64.9 (15.3)	63.8 (14.8)	64.3 (15.0)
Median	60.5	59.5	60.0
Min, max	45.0, 103.0	44.0, 100.0	44.0, 103.0
Height (cm)			
n	38	46	84
Mean (SD)	168.5 (9.7)	167.1 (10.7)	167.7 (10.2)
Median	168.0	166.5	167.0
Min, max	146.0, 190.0	150.0, 189.0	146.0, 190.0
BMI (kg/m^2)			
n	38	46	84
Mean (SD)	22.64 (3.44)	22.67 (3.86)	22.65 (3.65)
Median	22.31	22.26	22.26
Min, max	16.54, 30.61	17.10, 35.03	16.54, 35.03
BMI z-score (subjects ≤20 years old at parent study baseline)			
n	4	9	13
Mean (SD)	0.41 (0.64)	0.15 (1.27)	0.23 (1.09)
Median	0.24	-0.05	-0.03
Min, max	-0.13, 1.28	-1.39, 2.20	-1.39, 2.20

- 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.

CHMP comment

Baseline demographics and disease characteristics are nearly the same as for the parent study. It appears that 7 subjects from Study 104 did not participate in Study 110, 5 from the control arm and 2 from the treatment arm. Slight differences in baseline demographics and characteristics are likely caused by the absence of these subjects.

The mean age in Part A was 37.9 years and 36.3 year in Part B. The number of adolescents is not provided. However, in the parent study 9 adolescents were enrolled in the control group and 15 in the ELX/TEZ/IVA group.

Number analysed

The final number of subjects in each analysis set is provided in Table 10 and Table 11.

Table 10 Part A Analysis Populations

	Control in Study 104	ELX/TEZ/IVA in Study 104	Any ELX/TEZ/IVA
OL All Subjects Set for Part A	121	130	251
OL Full Analysis Set for Part A	121	130	251
OL Safety Set for Part A	121	130	251

Source: Table 14.1.1

ELX: elexacaftor; IVA: ivacaftor; OL: open-label; OLS: open-label study; TEZ: tezacaftor

Notes: OL All Subjects Set for Part A was defined as all subjects who were enrolled (defined as subject having data in the clinical database for the OLS) in the OLS Part A; OL Full Analysis Set for Part A was defined as all enrolled subjects who received at least 1 dose of study drug in the OLS Part A (treatment label is based on the treatment the subjects were assigned to in the parent study); OL Safety Set for Part A was defined as all subjects who received at least 1 dose of study drug in the OLS Part A (subjects were assigned based on parent study actual treatment).

Table 11 Part B Analysis Populations

	Control in Study 104	ELX/TEZ/IVA in Study 104	Any ELX/TEZ/IVA
OL All Subjects Set for Part B	38	46	84
OL Full Analysis Set for Part B	38	46	84
OL Safety Set for Part B	38	46	84

Source: Table 14.1.1b

ELX: elexacaftor; IVA: ivacaftor; OL: open-label; OLS: open-label study; TEZ: tezacaftor

Notes: Subjects in certain countries who completed Part A had the opportunity to participate in Part B. OL All Subjects Set for Part B was defined as all subjects who were enrolled (defined as subject having data in the clinical database for the OLS) in the OLS Part B; OL Full Analysis Set for Part B was defined as all enrolled subjects who received at least 1 dose of study drug in the OLS Part B (treatment label is based on the treatment the subjects were assigned to in the parent study); OL Safety Set for Part B was defined as all subjects who received at least 1 dose of study drug in the OLS Part B (subjects were assigned based on parent study actual treatment).

CHMP comment

The intended sample size of 250 for Part A was reached. Of these 250 subjects, 84 were included in Part B. However, only one of them completed the study.

Efficacy results

Efficacy results are only presented for Part A; **efficacy was not assessed in Part B**.

A summary of key efficacy results is presented in Table 12.

Table 12 Study 110 OL Week 96 Analysis: Secondary Efficacy Analyses (OL-FAS for Part A)

Analysis	Statistic	OL Week 96 Control in Study 104 N = 126	OL Week 96 ELX/TEZ/IVA in Study 104 N = 132
Absolute change from parent study baseline in $ppFEV_1$ (percentage points) at OL Week 96	n	80	96
	LS mean	4.1	3.7
	95% CI of LS mean	(2.5, 5.7)	(2.2, 5.2)
Absolute change from parent study baseline in SwCl (mmol/L) at OL Week 96	n	90	96
	LS mean	-23.0	-22.6
	95% CI of LS mean	(-25.8, -20.1)	(-25.4, -19.9)
Absolute change from parent study baseline in BMI (kg/m2) at OL Week 96	n	97	110
	LS mean	1.15	0.83
	95% CI of LS mean	(0.84, 1.45)	(0.54, 1.11)
Absolute change from parent study baseline in BMI z-score[a] at OL Week 96	n	7	11
	LS mean	0.11	0.40
	95% CI of LS mean	(-0.17, 0.40)	(0.17, 0.62)
Absolute change from parent study baseline in weight (kg) at OL Week 96	n	97	110
	LS mean	3.6	2.9
	95% CI of LS mean	(2.7, 4.6)	(2.0, 3.8)
Absolute change from parent study baseline in CFQ-R RD score (points) at OL Week 96	n	97	111
	LS mean	7.2	8.1
	95% CI of LS mean	(4.1, 10.4)	(5.1, 11.1)

Source: Tables 14.2.1.2, 14.2.2.2, 14.2.3.2, 14.2.4.2, 14.2.5.2, and 14.2.6.2

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire – Revised; aCSR: abbreviated clinical study report; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size (parent study FAS); OL: open-label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For further details on secondary efficacy endpoints, refer to respective sections in the aCSR.

[a] BMI z-score was analyzed for subjects ≤20 years old on the date of informed consent in the parent study.

More detailed results for the efficacy endpoints are discussed below.

Absolute change from baseline in ppFEV1:

The analysis of absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline is presented in Table 13 and Figure 2. This analysis was conducted with the clinic spirometry data only.

For subjects who received control treatment in Study 104, after initiation of ELX/TEZ/IVA in Study 110, rapid improvements in ppFEV1 were observed and sustained through OL Week 96. The least squares (LS) mean absolute change in ppFEV1 from parent study baseline at OL Week 96 was 4.1 percentage points (95% CI: 2.5, 5.7).

For subjects who received ELX/TEZ/IVA in Study 104, improvements in ppFEV1 were sustained through OL Week 96. The LS mean absolute change in ppFEV1 from parent study baseline at OL Week 96 was 3.7 percentage points (95% CI: 2.2, 5.2).

Table 13 MMRM Analysis of Absolute Change from Parent Study Baseline in ppFEV1 (%) at OL Week 96 (Study 104 FAS and OL-FAS for Part A)

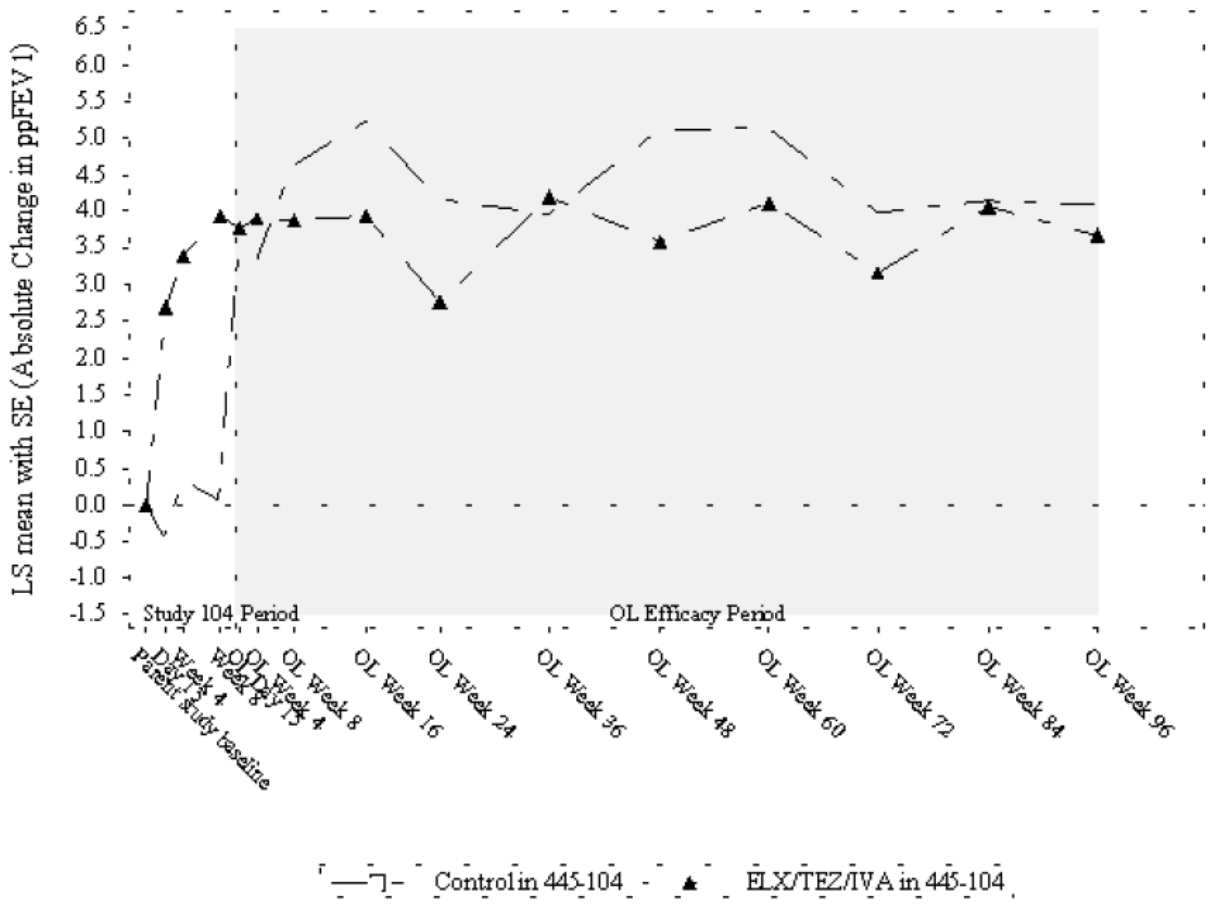
	Control in Study 104 N = 126	**ELX/TEZ/IVA in Study 104 N = 132**
Parent study baseline		
n	126	132
Mean (SD)	68.1 (16.4)	67.1 (15.7)
Absolute change at OL Week 96		
n	80	96
LS mean (SE)	4.1 (0.8)	3.7 (0.8)
95% CI of LS mean	(2.5, 5.7)	(2.2, 5.2)

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 (parent study FAS); OL: open-label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study SwCl, and comparator group of the parent study (IVA versus TEZ/IVA) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Figure 2 MMRM Analysis of Absolute Change From Parent Study Baseline in ppFEV1 (Percentage Points) at Each Visit Up to OL Week 96 (Study 104 FAS and OL-FAS for Part A)



Source: Figure 14.2.1

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

Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study SwCl, and comparator group of the parent study (IVA versus TEZ/IVA) 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.

Absolute Change in Sweat Chloride

The analysis of absolute change in SwCl in presented in Table 14 and Figure 3. For subjects who received control treatment in Study 104, after initiation of ELX/TEZ/IVA in Study 110, rapid improvements in SwCl were observed and sustained through OL Week 96. The LS mean absolute change in SwCl from parent study baseline at OL Week 96 was -23.0 mmol/L (95% CI: -25.8, -20.1).

For subjects who received ELX/TEZ/IVA in Study 104, improvements in SwCl were sustained through OL Week 96. The LS mean absolute change in SwCl from parent study baseline at OL Week 96 was -22.6 mmol/L (95% CI: -25.4, -19.9).

Table 14 MMRM Analysis of Absolute Change From Parent Study Baseline in SwCl (mmol/L) at OL Week 96 (Study 104 FAS and OL-FAS for Part A)

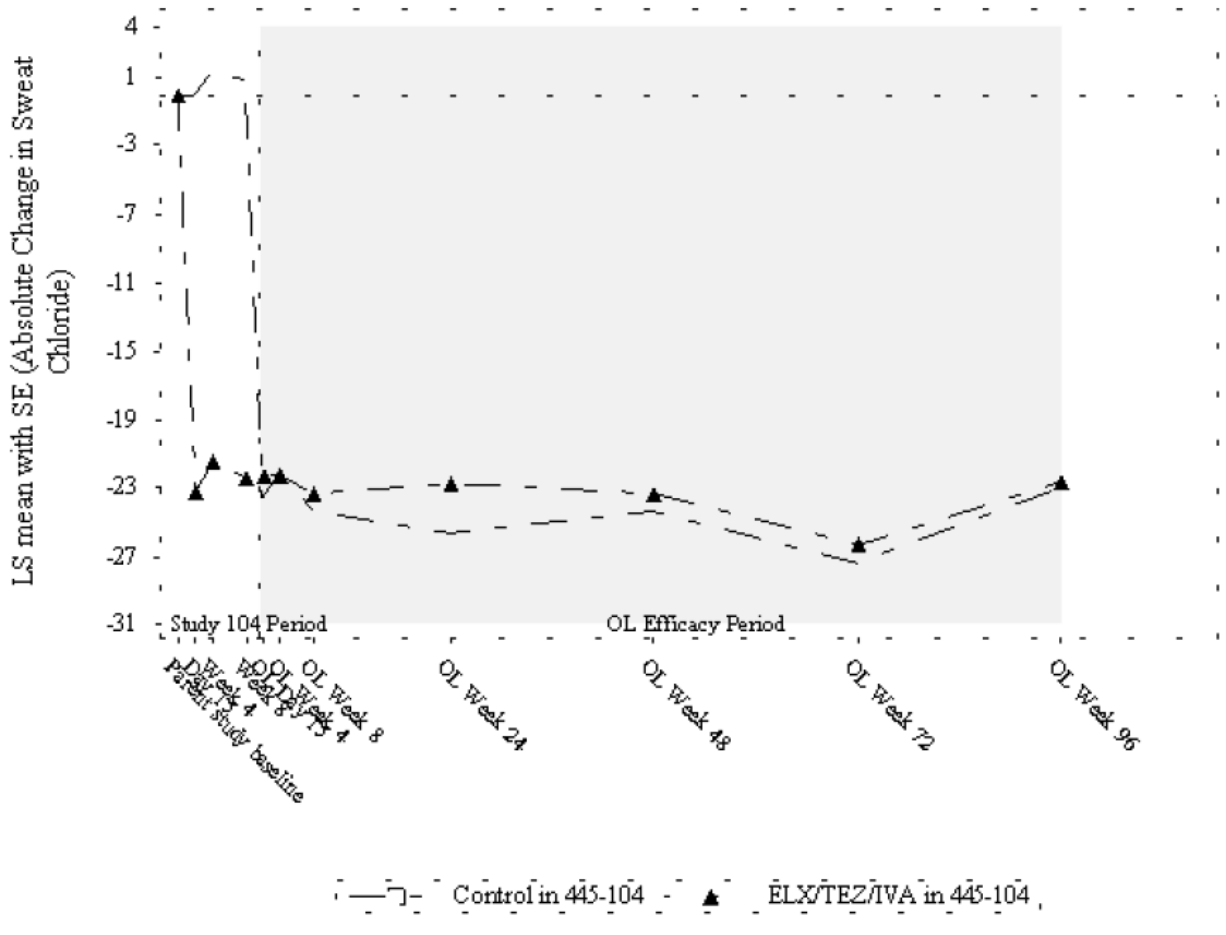
	Control in Study 104 N = 126	**ELX/TEZ/IVA in Study 104 N = 132**
Parent study baseline		
n	126	132
Mean (SD)	56.4 (25.5)	59.5 (27.0)
Absolute change at OL Week 96		
n	90	96
LS mean (SE)	-23.0 (1.4)	-22.6 (1.4)
95% CI of LS mean	(-25.8, -20.1)	(-25.4, -19.9)

Source: Table 14.2.2.2

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 (parent study FAS); OL: open-label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study SwCl, and comparator group of the parent study (IVA versus TEZ/IVA) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Figure 3 MMRM Analysis of Absolute Change From Parent Study Baseline in SwCl (mmol/L) at Each Visit up to OL Week 96 (Study 104 FAS and OL-FAS for Part A)



Source: Figure 14.2.2

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

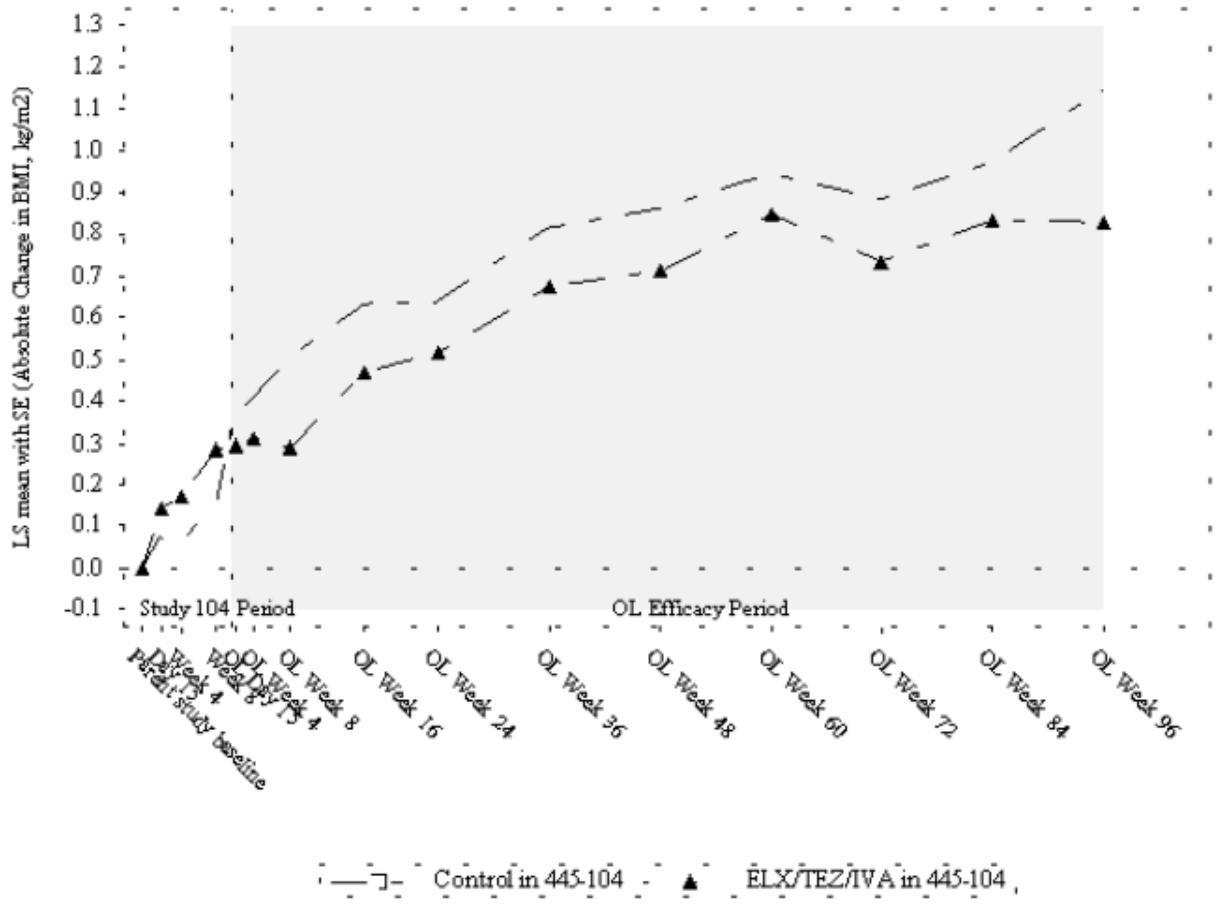
Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study SwCl, and comparator group of the parent study (IVA versus TEZ/IVA) 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.

Absolute Change in BMI

For subjects who received control treatment in Study 104, after initiation of ELX/TEZ/IVA in Study 110, rapid increases in BMI were observed and maintained through OL Week 96 (Figure 4). The LS mean absolute change in BMI from parent study baseline at OL Week 96 was 1.15 kg/m2 (95% CI: 0.84, 1.45).

For subjects who received ELX/TEZ/IVA in Study 104, increases in BMI were maintained through OL Week 96. The LS mean absolute change in BMI from parent study baseline at OL Week 96 was 0.83 kg/m2 (95% CI: 0.54, 1.11).

Figure 4 MMRM Analysis of Absolute Change From Parent Study Baseline in BMI (kg/m2) at Each Visit up to OL Week 96 (Study 104 FAS and OL-FAS for Part A)



Source: Figure 14.2.3

BMI: body mass index; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open-label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

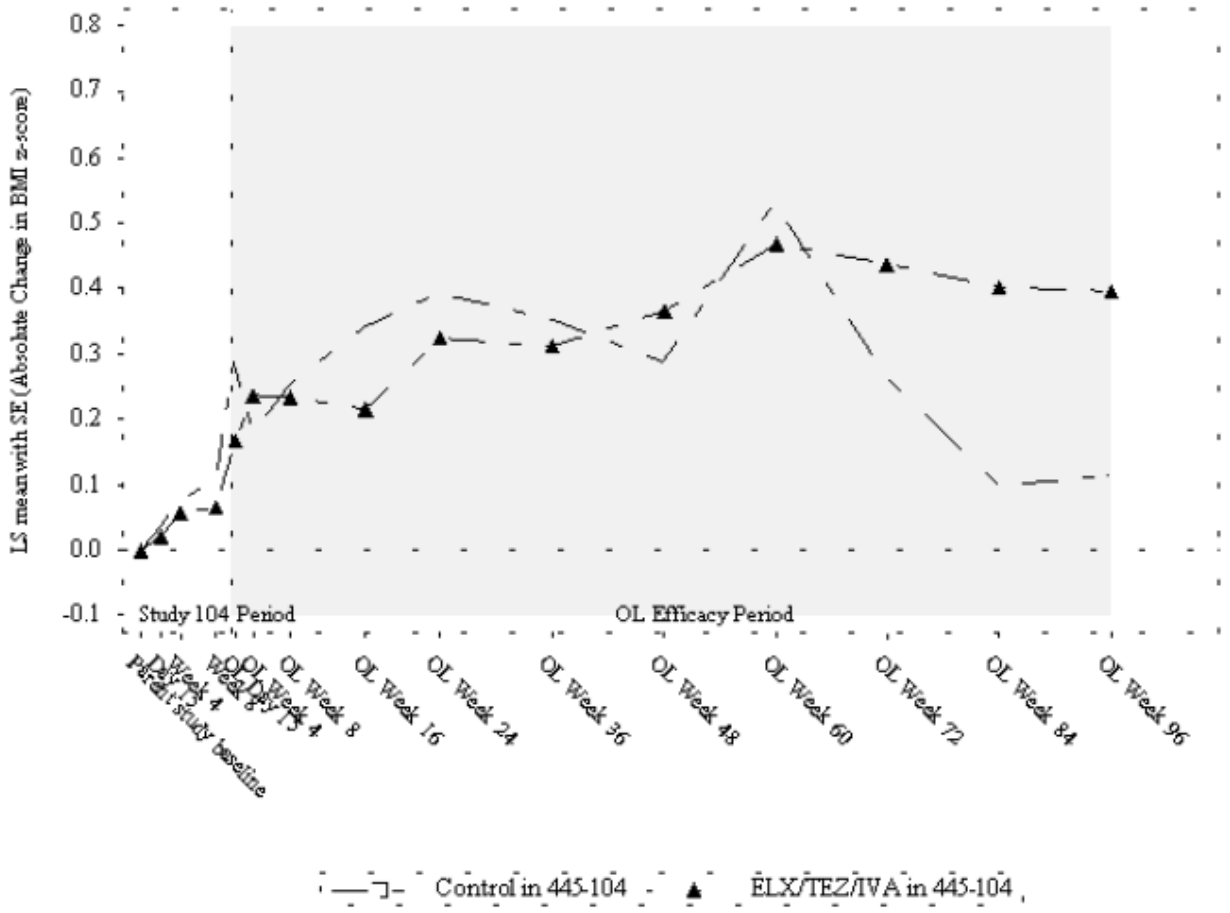
Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study baseline SwCl, and comparator group of the parent study (IVA versus TEZ/IVA) 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.

Absolute Change in BMI z-score

For subjects who received control treatment in Study 104, after initiation of ELX/TEZ/IVA in Study 110, the LS mean absolute change in BMI z-score from parent study baseline at OL Week 96 was 0.11 (95% CI: -0.17, 0.40) (Figure 5).

For subjects who received ELX/TEZ/IVA in Study 104, increases in BMI z-score were maintained through OL Week 96. The LS mean absolute change in BMI z-score from parent study baseline at OL Week 96 was 0.40 (95% CI: 0.17, 0.62).

Figure 5 MMRM Analysis of Absolute Change From Parent Study Baseline in BMI z-score (For Subjects ≤20 Years of Age at Parent Study Baseline) at Each Visit up to OL Week 96 (Study 104 FAS and OL-FAS for Part A)



Source: Figure 14.2.4

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

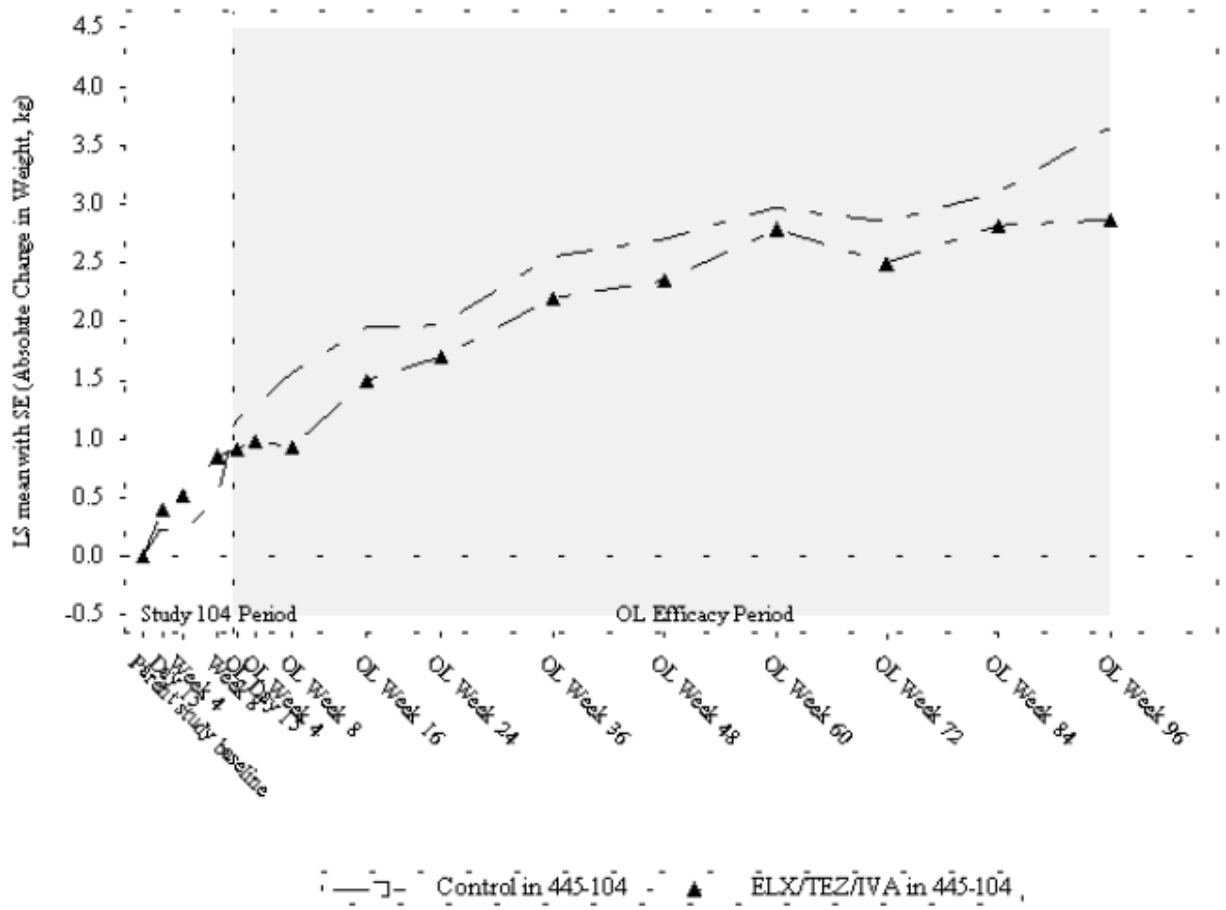
Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study baseline SwCl, and comparator group (IVA versus TEZ/IVA) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetric covariance structure was used to model the within-subject errors.

Absolute Change in Body Weight

For subjects who received control treatment in Study 104, after initiation of ELX/TEZ/IVA in Study 110, rapid increases in weight were observed and maintained through OL Week 96 (Figure 6). The LS mean absolute change in weight from parent study baseline at OL Week 96 was 3.6 kg (95% CI: 2.7, 4.6).

For subjects who received ELX/TEZ/IVA in Study 104, increases in weight were maintained through OL Week 96. The LS mean absolute change in weight from parent study baseline at OL Week 96 was 2.9 kg (95% CI: 2.0, 3.8).

Figure 6 MMRM Analysis of Absolute Change From Parent Study Baseline in Weight (kg) at Each Visit Up To OL Week 96 (Study 104 FAS and OL-FAS for Part A)



Source: Figure 14.2.5

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

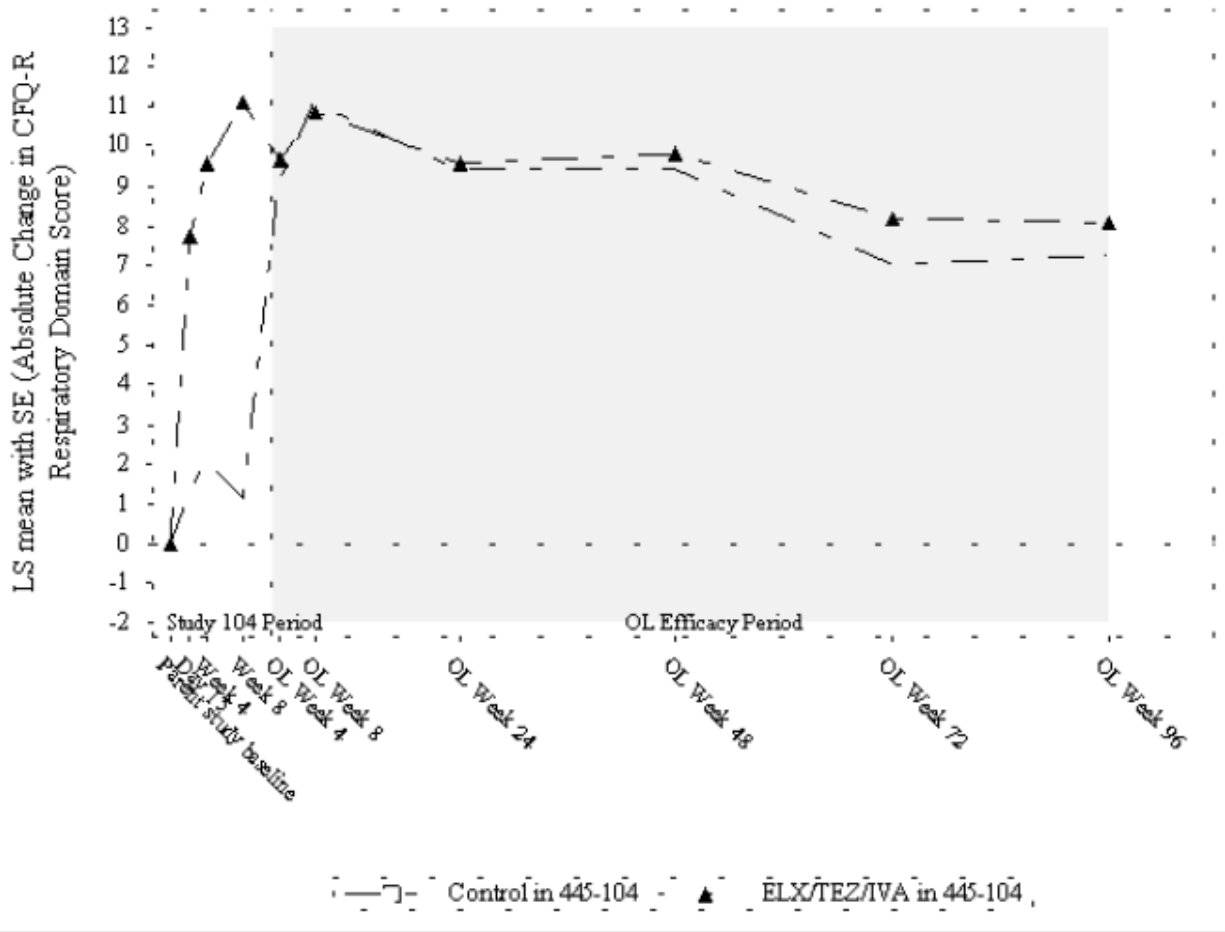
Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study baseline SwCl, and comparator group (IVA versus TEZ/IVA) 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.

Absolute Change From Baseline in CFQ-R RD Score

For subjects who received control treatment in Study 104, after initiation of ELX/TEZ/IVA in Study 110, improvements in CFQ-R RD score were observed and maintained through OL Week 96 (Figure 7). The LS mean absolute change in CFQ-R RD score from parent study baseline at OL Week 96 was 7.2 points (95% CI: 4.1, 10.4).

For subjects who received ELX/TEZ/IVA in Study 104, improvements in CFQ-R RD score were maintained through OL Week 96. The LS mean absolute change in CFQ-R RD score was 8.1 points (95% CI: 5.1, 11.1).

Figure 7 MMRM Analysis of Absolute Change From Parent Study Baseline in CFQ-R RD Score at Each Visit Up To OL Week 96 (Study 104 FAS and OL-FAS for Part A) – Clinic and Home Assessed



Source: Figure 14.2.6

CFQ-R: Cystic Fibrosis Questionnaire–Revised; 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 (parent study FAS); OL: open-label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For Parent Study Efficacy Period, MMRM was the same as parent study analysis. For OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, and parent study baseline $ppFEV_1$, parent study baseline SwCl, and comparator group (IVA versus TEZ/IVA) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors. The model was applied to CFQ-R data obtained in clinic and at home. The CFQ-R RD score from the Children Ages 12 and 13 Version and Adolescent and Adults Version were pooled for analysis.

CHMP comment

In the current study, the absolute change in ppFEV1 for subjects who received control treatment in Study 104 was comparable to that of patients in the ELX/TEZ/IVA arm of Study 104. During the 96-week study period, ppFEV1 improvements were stable in both groups. Similar results were obtained for the absolute change in SwCl. CFQ-R RD scores decreased slightly over the course of Study 110, but were nevertheless considerably higher compared to the baseline of the parent study. Subjects who received control treatment during the parent study had a slightly bigger increase in body weight (and consequently BMI) than subjects who had received ELX/TEZ/IVA during study 104. The BMI z-score did

not seem to be maintained at the end of the study (>week 60) in subjects that received control treatment during the parent study. The Applicant clarified that unlike BMI, BMI z-score was only assessed for subjects ≤20 years of age at parent study baseline (n=14 subjects who received control treatment in the parent study and n=18 subjects who received ELX/TEZ/IVA in the parent study). At open-label Week 60 and all subsequent visits, there were only 6 to 7 non-missing data points for subjects who received control treatment in the parent study and 11 to 14 non-missing data points for subjects who received ELX/TEZ/IVA in the parent study. Given such small sample sizes, variation in the mean change from baseline values is expected, and therefore BMI z-score data in Study VX18-445-110 should be interpreted with caution.

Overall, efficacy results obtained in parent study 104 could be replicated and sustained over the full 96-week study period.

Safety results

Safety population

The safety set (OL Safety Set [OL-SS]) consisted of all subjects who received at least 1 dose of study drug in the OLS. Safety data is provided per study part (OL-SS Part A and OL-SS Part B).

Exposure

The OL Safety Set for **Part A** included 251 subjects who had a mean exposure duration of 89.3 weeks, representing 467.1 patient-years of exposure (Table 15)

Table 15 Summary of Exposure – OL Safety Period (OL-SS Part A)

	Control in Study 104 N = 121	ELX/TEZ/IVA in Study 104 N = 130	Any ELX/TEZ/IVA N = 251
Total exposure (patient-weeks)	10592.0	11826.6	22418.6
Total exposure (patient-years)	220.7	246.4	467.1
Exposure duration (weeks)			
n	121	130	251
Mean (SD)	87.5 (22.2)	91.0 (17.7)	89.3 (20.0)
Median	96.0	96.0	96.0
Min, max	1.0, 98.4	3.0, 103.0	1.0, 103.0
Exposure duration by interval, n (%)			
≤24 weeks	6 (5.0)	2 (1.5)	8 (3.2)
>24 to ≤48 weeks	5 (4.1)	5 (3.8)	10 (4.0)
>48 to ≤72 weeks	6 (5.0)	4 (3.1)	10 (4.0)
>72 to ≤96 weeks	57 (47.1)	64 (49.2)	121 (48.2)
>96 weeks	47 (38.8)	55 (42.3)	102 (40.6)

Source: Table 14.1.7

ELX: elexacaftor; IVA: ivacaftor; max: maximum; min: minimum; n: size of subsample; N: total sample size; OL: open-label; TEZ: tezacaftor

Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects in Part A. Duration of study drug exposure (weeks) = (last dose date of study drug in the OLS – first dose date of study drug in the OLS + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = (last dose date of study drug in the OLS - first dose date of study drug in the OLS + 1)/336, regardless of study drug interruption; 1 year = 48 weeks = 336 days.

The OL Safety Set for **Part B** included 84 subjects who had a mean exposure duration of 22.9 weeks, representing 40.1 patient-years of exposure (Table 16). The majority of subjects discontinued treatment and the study due to commercial drug availability.

Table 16 Summary of Exposure – OL Safety Period (OL-SS Part B)

	Control in Study 104 N = 38	ELX/TEZ/IVA in Study 104 N = 46	Any ELX/TEZ/IVA N = 84
Total exposure (patient weeks)	913.0	1013.3	1926.3
Total exposure (patient years)	19.0	21.1	40.1
Exposure duration (weeks)			
n	38	46	84
Mean (SD)	24.0 (8.9)	22.0 (10.4)	22.9 (9.7)
Median	24.0	23.3	23.4
Min, max	9.6, 48.0	10.9, 44.4	9.6, 48.0

Source: Table 14.1.7b

ELX: elexacaftor; IVA: ivacaftor; max: maximum; min: minimum; n: size of subsample; N: total sample size; OL: open-label; TEZ: tezacaftor

Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects in Part B. Duration of study drug exposure (weeks) = (last dose date of study drug in Part B – first dose date of study drug in Part B + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = (last dose date of study drug in Part B - first dose date of study drug in Part B + 1)/336, regardless of study drug interruption; 1 year = 48 weeks = 336 days.

Adverse events

In Study 110 **Part A**, 241 (96.0%) subjects had at least 1 AE and 38 (15.1%) had at least 1 serious AE (SAE). See Table 17.

The majority of subjects had AEs that were mild or moderate in severity. Overall, 20 (8.0%) subjects had 1 or more severe AEs, 2 (0.8%) subjects had a life-threatening AE, and there was 1 death due to an AE of colon cancer that was assessed as unlikely related to study drug. Seventeen (6.8%) subjects interrupted ELX/TEZ/IVA due to AEs, and 13 (5.2%) subjects discontinued ELX/TEZ/IVA due to AEs.

Table 17 Overview of AEs – OL Safety Period (OL-SS Part A)

	Any ELX/TEZ/IVA N = 251	
	n (%)	Events/100PY
Number of AEs (Total)	2776	--
Total duration of safety analysis period in 100 PY	--	4.71
Subjects with any AEs	241 (96.0)	589.36
Subjects with AEs by strongest relationship		
Not related	88 (35.1)	--
Unlikely related	58 (23.1)	--
Possibly related	78 (31.1)	--
Related	17 (6.8)	--
Subjects with AEs by maximum severity		
Mild	81 (32.3)	--
Moderate	138 (55.0)	--
Severe	20 (8.0)	--
Life-threatening	2 (0.8)	--
Missing	0	--
Subjects with AEs leading to study drug discontinuation	13 (5.2)	5.52
Subjects with AEs leading to study drug interruption	17 (6.8)	6.58
Subjects with Grade 3/4 AEs[a]	22 (8.8)	9.13
Subjects with related AEs	95 (37.8)	58.17
Subjects with SAEs	38 (15.1)	13.38
Subjects with related SAEs	2 (0.8)	1.06
Subjects with AEs leading to death	1 (0.4)	0.21

Source: Table 14.3.1.1

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; PY: patient-year; SAE: serious adverse event; TEZ: tezacaftor

Notes: MedDRA Version 24.1 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. An AE with relationship missing was counted as related.

[a] Grade 3 indicates events of severe intensity; Grade 4 indicates events that were life-threatening.

In Study 110 **Part B**, 62 (73.8%) subjects had at least 1 AE and 3 (3.6%) had at least 1 SAE; no SAE was assessed as related to study drug. See Table 18.

The majority of subjects had AEs that were mild (31.0%) or moderate (41.7%) in severity (Table 14.3.1.1b). Overall, 1 (1.2%) subject had a severe AE. There were no deaths, or AEs that led to study drug interruption or discontinuation.

Table 18 Overview of AEs – OL Safety Period (OL-SS Part B)

	Any ELX/TEZ/IVA N = 84
	n (%)
Number of AEs (Total)	244
Subjects with any AEs	62 (73.8)
Subjects with AEs by strongest relationship	
Not related	51 (60.7)
Unlikely related	10 (11.9)
Possibly related	1 (1.2)
Related	0
Subjects with AEs by maximum severity	
Mild	26 (31.0)
Moderate	35 (41.7)
Severe	1 (1.2)
Life-threatening	0
Missing	0
Subjects with AEs leading to study drug discontinuation	0
Subjects with AEs leading to study drug interruption	0
Subjects with Grade 3/4 AEs[a]	1 (1.2)
Subjects with related AEs	1 (1.2)
Subjects with SAEs	3 (3.6)
Subjects with related SAEs	0
Subjects with AEs leading to death	0

Source: Table 14.3.1.1b

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; PY: patient-year; SAE: serious adverse event; TEZ: tezacaftor

Notes: MedDRA Version 25.1 was used. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. An AE with relationship missing was counted as related.

[a] Grade 3 indicates events of severe intensity; Grade 4 indicates events that were life-threatening.

CHMP comment

The percentage of subjects with any AE as well as Grade 3/4 AEs, related AEs and SAEs was higher in Part A of the study than in Part B. There were also more AEs related to study drug in Part A. This difference may be due to the large number of patients who discontinued treatment in Part B.

The percentage of subjects with AEs is considerably higher than in the parent study. In the parent study, 66.7% of the subjects in the treatment arm and 65.9% in the control arm had an AE, while this frequency increased to 96% in Study 110. In the treatment arm of the parent study, 3.8% of the AEs were Grade 3/4, 24.2% were considered related, and 3.8% were SAEs, compared to 8.8%, 37.8% and 15.1% respectively in Study 110. However, the parent study had a treatment period of only 8 weeks, so higher percentages of AEs in Study 110 are not unexpected. The safety pattern is comparable to that observed in other long-term safety studies.

Common Adverse Events

Table 19 shows all AEs that occurred in at least 10% of subjects in Study 110 **Part A**, summarised by PT. Most common AEs were headache, infective pulmonary exacerbation of CF, cough, and COVID-19.

Table 19 AEs With an Incidence ≥10% by PT (OL-SS Part A)

	Any ELX/TEZ/IVA N = 251	
PT	**n (%)**	**Events/100PY**
Subjects with any AEs	241 (96.0)	589.36
Headache	71 (28.3)	39.91
Infective pulmonary exacerbation of cystic fibrosis	66 (26.3)	26.96
Cough	65 (25.9)	20.38
COVID-19	53 (21.1)	11.46
Diarrhoea	48 (19.1)	15.71
Oropharyngeal pain	42 (16.7)	11.89
Fatigue	40 (15.9)	11.04
Nasopharyngitis	40 (15.9)	12.74
Pyrexia	36 (14.3)	9.13
Sputum increased	34 (13.5)	12.31
Dyspnoea	29 (11.6)	8.07
Anxiety	28 (11.2)	6.79
Nausea	28 (11.2)	17.62
Vaccination complication	28 (11.2)	9.77
Arthralgia	27 (10.8)	7.01
Blood creatine phosphokinase increased	26 (10.4)	5.52

Source: Table 14.3.1.3

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; OL: open-label; PT: Preferred Term; PY: patient-years; TEZ: tezacaftor

Notes: MedDRA Version 24.1 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency by PT.

AEs that occurred in at least 10% of subjects in Study 110 **Part B** were COVID-19 and infective pulmonary exacerbation (PEx) of CF, which both occurred in 17 subjects (20.2%).

CHMP comment

Overall, AEs were consistent with common manifestations or CF disease, common illnesses in CF subjects 12 years of age and older, or the known safety profile of ELX/TEZ/IVA. In general, frequencies are somewhat higher than in parent study 104, but this may be caused by the longer treatment period.

Quite a large number of subjects experienced anxiety (28 [11.2%] in Part A) during study 110. Of these 28 events, 9 (3.6%) were considered possibly related and 2 (0.8%) related. AEs of anxiety were not seen during the initial marketing authorisation, while in parent study 104, only one subject in the control arm had an AE of anxiety. In an ongoing procedure (EMEA/H/C/005269/X/0033/G), the Applicant is requested to monitor and analyse psychiatric-related AEs in the PSURs for all age groups.

Severity of Adverse Events

In **Part A**, the majority of subjects had AEs that were mild (32.3%) or moderate (55.0%) in severity (Table 17). Overall, 20 (8.0%) subjects had 1 or more severe AEs, and 2 (0.8%) had a life-threatening AE. One life-threatening AE was a spontaneous pneumothorax, while the other one was colon cancer. Both were considered not to be related to ELX/TEZ/IVA by the investigator.

In **Part B**, there was only one severe AE (1.2%), all others were either mild (31.0%) or moderate (41.7%).

Relationship of Adverse Events

Overall, 17 (6.8%) subjects of **Part A** had an AE assessed by the investigator as related, and 78 (31.1%) subjects had an AE assessed by the investigator as possibly related (Table 17). AEs designated as related or possibly related that occurred in ≥3% of subjects were blood creatine phosphokinase increased (6.0%), alanine aminotransferase (ALT) increased (4.0%), aspartate aminotransferase (AST) increased (4.0%), rash (4.0%) and anxiety (4.4%).

In **Part B**, 1 (1.2%) subject had an AE assessed by the investigator as related.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There was 1 AE of colon cancer leading to death in **Part A**. This event was considered unlikely related to study drug. There were 38 (15.1%) subjects who had at least 1 SAE. SAEs occurring in ≥2 subjects in the OLS are presented in Table 20. Two subjects had related SAEs; 1 subject had SAEs of ALT increased (0.4%) and AST increased (0.4%), and the second subject had an SAE of suicidal ideation (0.4%).

Table 20 SAEs Occurring in ≥2 Subjects in the OLS by PT (OL-SS Part A)

	Any ELX/TEZ/IVA N = 251	
PT	**n (%)**	**Events/100PY**
Subjects with any SAEs	38 (15.1)	13.38
Infective pulmonary exacerbation of cystic fibrosis	16 (6.4)	5.31
Haemoptysis	3 (1.2)	0.85
Infective exacerbation of bronchiectasis	2 (0.8)	0.42
Pneumothorax spontaneous	2 (0.8)	0.42
Nephrolithiasis	2 (0.8)	0.42

Source: Table 14.3.2.1

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; PT: Preferred Term; PY: patient-years; SAE: serious adverse event; TEZ: tezacaftor

Notes: MedDRA Version 24.1 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency by PT.

Part B: There were no deaths. Three (3.6%) subjects had at least 1 SAE, which were pulmonary exacerbation, acute anterior chest pain with unknown aetiology, angiolipoma, neausea and vomiting, all occuring in only one subject. Of these, only the angiolipoma was considered possibly related.

CHMP comment

Overall, related AEs and SAEs were consistent with common CF manifestations and complications, the parent study and the known safety profile for ELX/TEZ/IVA (except for the AE of anxiety, which is discussed above). It is agreed that the event of colon cancer leading to death is unlikely related to study drug.

Study Drug Discontinuation

Overall, 13 (5.2%) subjects in **Part A** had AEs that led to treatment discontinuation. AEs leading to treatment discontinuation in ≥2 subjects were liver-related events (including alanine transaminase ALT increased in 4 [1.6%] subjects, AST increased in 3 [1.2%] subjects, and blood bilirubin increased in 3 [1.2%] subjects), anxiety (2 [0.8%] subjects), and insomnia (2 [0.8%] subjects).

In **Part B**, no subjects had AEs that led to study drug discontinuation.

Adverse Events That Led to Interruption of Study Drug

In **Part A**, 17 (6.8%) subjects had AEs that led to treatment interruption. AEs leading to treatment interruption occurring in at least 2 subjects were ALT increased (7 subjects), AST increased (7 subjects), blood creatine phosphokinase increased (3 subjects), gamma glutamyltransferase increased (2 subjects), and diarrhoea (2 subjects).

In **Part B**, no subjects had AEs that led to treatment interruption.

CHMP comment

The number of subjects who had AEs leading to drug interruption is comparable to what was seen during the initial marketing authorisation. However, there were slightly more treatment discontinuations due to AEs during study 110 (5.2%) compared with the studies of the initial procedure (where a maximum of 1.4% of subjects discontinued study drug). This difference is considered acceptable, considering the longer treatment duration and the fact that AEs leading to discontinuation were known AEs of ELX/TEZ/IVA (with the exception of anxiety, which was discussed above).

Adverse Events of Special Interest

Elevated Transaminase Events

In **Part A**, 17 subjects (6.8%) had at least 1 elevated transaminase event. Both ALT increased and AST increased occurred in 16 subjects (6.4%) each. The majority of events were mild or moderate in severity, whereas three events (1.2%) were severe. Elevated transaminases led to treatment discontinuation in 4 subjects (1.6%) and to treatment interruption in 8 subjects (3.2%).

Similar results were seen in **Part B**.

Rash Events

In **Part A**, 29 (11.6%) subjects had a rash event. The majority of events were mild or moderate in severity; one event was severe. No subject had a rash event that led to treatment discontinuation, and 2 (0.8%) subjects had a rash event that led to treatment interruption. One (0.4%) subject had a serious rash event (SAE of rash erythematous that resolved with treatment).

By sex, 18/124 female subjects (14.5%) and 11/127 male subjects (8.7%) had rash events. In female subjects, 6/42 subjects (14.3%) who used hormonal therapy and 12/82 subjects (14.6%) not using hormonal therapy had rash events.

There were no rash events in **Part B**.

CHMP comment

Elevated transaminases and rash are known AEs of ELX/TEZ/IVA. During the initial marketing application, a higher incidence of rash was seen in female subjects taking hormonal therapy compared with those not taking hormonal therapy in the ELX/TEZ/IVA arm. This trend was not observed in Study

104 and is also not seen in the current study. Hence, there are no new insights in the AESIs of elevated transaminases and rash.

Clinical Laboratory Evaluation

Chemistry (Part A)

Liver function tests (LFTs) are described above (see AESI elevated transaminase described above). There were no trends in mean values of other non-LFT chemistry parameters and no clinically significant trends in creatine kinase concentration levels were seen.

Haematology (Part A)

There were no trends observed in haematology parameters. AEs related to haematology were infrequent (PTs occurred in 1 to 2 subjects each), not serious and did not lead to treatment discontinuation or interruption.

Coagulation (Part A)

There were no trends or AEs related to coagulation assessments.

Urinalysis (Part A)

There were no trends in urinalysis results. AEs related to urinalysis were infrequent (most PTs occurred in 1 to 2 subjects each), not serious and did not lead to treatment discontinuation or interruption.

Vital signs (Part A)

The mean (SD) systolic and diastolic blood pressure increased from baseline through OL Week 96 by 2.6 (13.2) and 2.5 (9.4) mm HG, respectively. The mean pulse rate was variable over time. No subjects had AEs of decreased pulse rate. There were no trends in temperature, respiratory rate or pulse oximetry.

ECG (Part A)

The mean heart rate (HR) was variable over time, but consistent with pulse rate findings. The mean decreases in HR ranged from -0.3 to -1.7 beats per minute. No subject had AEs of HR decreased. There were no trends observed in other ECG parameters. AEs related to ECG findings or relevant cardiac disorders were infrequent (majority of PTs occurred in 1 to 2 subjects each). There were two cardiac disorder SAEs (i.e. atrial fibrillation and palpitations), but those were assessed as not related and did not lead to treatment discontinuation or interruption.

Ophthalmologic Examinations (Part A)

There were two mild, nonserious and possibly related AEs (one cataract and one lenticular opacities). No treatment was required.

Overall, laboratory findings in **Part B** were consistent with or less frequent/severe than in Part A of the study.

CHMP comment

In general, clinical laboratory findings are in line with those observed in the parent study.

2.3.3. Discussion on clinical aspects

Kaftrio obtained approval by the EMA on 21 August 2020. Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of CF in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The MAH now

submitted the results of a stand-alone study, Study VX18-445-110 ("110"), as per requirement of Article 46 of the "Paediatric Regulation" (EC) 1901/2006.

Study 110 is a Phase 3, multicenter, open-label study (OLS) in subjects with CF 12 years of age and older, heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes), who completed Study VX18-445-104 (Study 104). The study consisted of two parts: Part A (96 weeks Treatment Period) and, in certain countries, Part B (48 weeks Treatment Period), followed by a 4-week Safety Follow-up Period. During the Treatment Period, patients received standard ELX/TEZ/IVA treatment as described in the SmPC. In- and exclusion criteria were the same as for parent Study 104 and thus considered acceptable.

Primary endpoint was the safety and tolerability of long-term treatment with ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry. This endpoint is appropriate for an open-label extension study. Secondary endpoints included absolute changes in efficacy measures, such as ppFEV1, SwCl, body measures and CFQ-R RD scores, which are considered relevant outcome measures for CF treatment.

A total of 251 patients were included in Part A (250 subjects were planned), of these, 84 patients rolled-over to Part B. Only 1 of these 84 subjects completed the study; 81 subjects (96.4%) discontinued treatment and the study due to the availability of the commercial drug. As such, results for Part A are considered most important for this procedure. The mean age in Part A was 37.9 years (including approximately 14 adolescents) and 36.3 year in Part B.

Efficacy results (only Part A) were generally in line with those observed in the parent study. Subjects who received control treatment during Study 104 had comparable changes in efficacy measures as those who received ELX/TEZ/IVA during the parent study. In addition, efficacy parameters were relatively stable during the 96-week study period. However, while the absolute change in body weight and BMI increased over the course of the study, the BMI z-score did not seem to be maintained at the end of the study (>week 60) in subjects that received control treatment during the parent study. The Applicant clarified that BMI z- score was, unlike BMI, only assessed for a small subgroup of patients ≤ 20 years. From week 60 onwards there were only very few nonmissing data points available. Hence, BMI z-score data in Study 110 should be interpreted with caution.

Adverse events were generally mild or moderate in severity. There were two life-threatening AEs and one AE leading to death in Part A, but these were considered unrelated to the study drug. Most common AEs were headache, infective pulmonary exacerbation of CF, cough, and COVID-19, which all occurred in more than 20% of the subjects. AEs leading to study drug interruption or discontinuation were rare and mainly liver-related events. Frequencies of AEs, Grade 3/4 AEs, related AEs and SAEs were higher compared with the parent study. This likely reflects the longer treatment duration in Study 110 (96 weeks vs. 8 weeks in the parent study). The safety profile is generally consistent with other open-label extensions studies. Quite a large number of subjects experienced anxiety (28 [11.2%] in Part A) compared to previous studies. In an ongoing procedure (EMEA/H/C/005269/X/0033/G), a request for post-approval follow-up of the AE of anxiety was already demanded. There were no new insights in the AESIs of elevated transaminases and rash. However, in general, AEs were consistent with common manifestations and complications of CF disease in subjects 12 years of age and older, or the known safety profile of ELX/TEZ/IVA.

Conclusion

The benefit-risk evaluation of Kaftrio remains positive. No new safety signals have been observed in Study 110 and results for secondary efficacy endpoints are also in line with previous studies. No update of the product information is considered needed at present.

3. Rapporteur's overall conclusion and recommendation

The benefit-risk evaluation of Kaftrio remains positive. No new safety signals have been observed in CF patients aged 12 years and older with F/G and F/RF genotypes treated with ELX/TEZ/IVA in Study 110. No update of the product information is considered needed at present.

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Other concern

1. While the absolute change in body weight and BMI increased over the course of Study 110, the BMI z-score did not seem to be maintained at the end of the study (>week 60) in subjects that received control treatment during the parent study. The Applicant is asked to give potential explanations for these results.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

Unlike BMI, which was assessed in all subjects, BMI z-score was only assessed for subjects ≤20 years of age at parent study baseline (N = 14 subjects who received control treatment in the parent study and N = 18 subjects who received ELX/TEZ/IVA in the parent study). See Table 1 for details.

Table 1 **MMRM Analysis of Absolute Change From Parent Study Baseline in BMI Z-score at Each Visit for Subjects ≤20 Years at Parent Study Baseline (Study 104 FAS and OL FAS for Study 110 Part A)**

	Control in Study 104	ELX/TEZ/IVA in Study 104
Parent efficacy period based on Study 104 FAS		
N	14	18
Parent study baseline		
n	14	18
Mean (SD)	-0.16 (0.74)	-0.08 (1.11)
Absolute change at Day 15		
n	12	14
LS mean (SE)	0.03 (0.05)	0.02 (0.04)
95% CI of LS mean	(-0.07, 0.14)	(-0.06, 0.10)
Absolute change at Week 4		
n	12	15
LS mean (SE)	0.07 (0.05)	0.06 (0.04)
95% CI of LS mean	(-0.03, 0.18)	(-0.03, 0.14)
Absolute change at Week 8		
n	12	13
LS mean (SE)	0.11 (0.07)	0.07 (0.06)
95% CI of LS mean	(-0.03, 0.25)	(-0.06, 0.19)

	Control in Study 104	ELX/TEZ/IVA in Study 104
OL Efficacy Period based on OL Full Analysis Set		
N	12	17
Absolute change at OL Day 15		
n	10	10
LS mean (SE)	0.29 (0.13)	0.17 (0.11)
95% CI of LS mean	(0.02, 0.55)	(-0.06, 0.40)
Absolute change at OL Week 4		
n	8	12
LS mean (SE)	0.18 (0.14)	0.24 (0.11)
95% CI of LS mean	(-0.10, 0.46)	(0.02, 0.46)
Absolute change at OL Week 8		
n	8	13
LS mean (SE)	0.25 (0.14)	0.23 (0.11)
95% CI of LS mean	(-0.02, 0.53)	(0.02, 0.45)
Absolute change at OL Week 16		
n	9	16
LS mean (SE)	0.34 (0.14)	0.22 (0.10)
95% CI of LS mean	(0.07, 0.61)	(0.01, 0.42)
Absolute change at OL Week 24		
n	10	15
LS mean (SE)	0.39 (0.13)	0.32 (0.11)
95% CI of LS mean	(0.12, 0.66)	(0.11, 0.54)
Absolute change at OL Week 36		
n	10	14
LS mean (SE)	0.35 (0.13)	0.31 (0.11)
95% CI of LS mean	(0.09, 0.62)	(0.09, 0.53)
Absolute change at OL Week 48		
n	9	14
LS mean (SE)	0.29 (0.14)	0.37 (0.11)
95% CI of LS mean	(0.01, 0.56)	(0.15, 0.58)
Absolute change at OL Week 60		
n	6	14
LS mean (SE)	0.53 (0.15)	0.47 (0.11)
95% CI of LS mean	(0.24, 0.82)	(0.25, 0.68)
Absolute change at OL Week 72		
n	7	13
LS mean (SE)	0.26 (0.14)	0.44 (0.11)
95% CI of LS mean	(-0.02, 0.55)	(0.22, 0.66)
Absolute change at OL Week 84		
n	7	13
LS mean (SE)	0.10 (0.14)	0.40 (0.11)

	Control in Study 104	ELX/TEZ/IVA in Study 104
95% CI of LS mean	(-0.19, 0.38)	(0.18, 0.62)
Absolute change at OL Week 96		
n	7	11
LS mean (SE)	0.11 (0.14)	0.40 (0.11)
95% CI of LS mean	(-0.17, 0.40)	(0.17, 0.62)

Source: Study 110/Table 14.2.4.2

BMI: body mass index; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed effect model of repeated measures; OL: open-label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study. For the parent study period, MMRM was the same as the parent study analysis. For the OL Efficacy Period, MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment*visit as fixed effects, and parent study baseline $ppFEV_1$, parent study baseline sweat chloride and comparator group of the parent study (IVA comparator versus TEZ/IVA comparator) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetry covariance structure was used to model the within-subject errors.

As shown above in Table 1, at open-label Week 60 and all subsequent visits, there were only 6 to 7 nonmissing data points for subjects who received control treatment in the parent study and 11 to 14 nonmissing data points for subjects who received ELX/TEZ/IVA in the parent study. Given such small sample sizes, variation in the mean change from baseline values is expected, and therefore BMI z-score data in Study VX18-445-110 should be interpreted with caution. Overall, the BMI z-score data are consistent for subjects who received control treatment in the parent study, in the context of the wide and overlapping 95% CIs at all visits.

Rapporteur's assessment

The clarification of the Applicant, i.e. that BMI z-score was analysed in a small subset of patients and that there were only few non-missing data points from week 60 onwards is acknowledged. It is agreed that BMI z-score data in Study 110 should be interpreted with caution. As such, no firm conclusions could be drawn based on the curves from week 60 onwards.

Conclusion

Issue resolved. The assessment report is updated accordingly.