EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/CHMP/188905/2022
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/P46/008

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

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATC	anatomic class
BMI	body mass index
Bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
CK	creatine kinase
COVID-19	coronavirus disease
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
ELX	elexacaftor
ETT	Early Termination of Treatment
F/MF	heterozygous for F508del and a CFTR minimal function mutation
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDC	fixed-dose combination
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor
IWRS	interactive web response system
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LFT	liver function test
LS	least squares
LUM	lumacaftor
max	maximum value
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
N	total sample size
n	size of subsample
N1	number of subjects with at least 1 non-missing measurement during the TE Period
NOS	not otherwise specified
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OE	ophthalmological examination
P	probability
PD	pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbation

P-gp	P-glycoprotein
PK	pharmacokinetics
PN	Preferred Name
ppFEV1	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QTcF	QT interval corrected by Fridericia's formula
r2	multiple correlation coefficient
RD	respiratory domain
RNA	ribonucleic acid
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	SI units (International System of Units)
SOC	System Organ Class
SwCl	sweat chloride
TBILI	total bilirubin
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
t-test	statistical test used when the independent variable is binary and the dependent variable is continuous
ULN	upper limit of normal
WHO-DD	World Health Organization-Drug Dictionary

1. Introduction

On 9-2-2022, the MAH submitted a completed paediatric study for Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF), 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

Kaftrio 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. Kaftrio obtained initially a marketing authorization 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 in 2020. In 2021, the indication was extended to patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Recently, the indication was extended to children with CF aged 6 years through 11.

Elexacaftor and tezacaftor are CFTR correctors and facilitate the cellular processing and trafficking of F508del-CFTR, leading to an increase in the amount of CFTR protein, while ivacaftor increases channel gating of the CFTR protein at the cell surface. The combined effect of elexacaftor, tezacaftor and ivacaftor results in increased CFTR activity as measured by CFTR chloride transport

The MAH stated that Study VX19-445-116, a Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study VX19-445-116, the following tablets were used:

- 100-mg ELX/50-mg TEZ/75-mg IVA fixed-dose combination (FDC) tablet
- 50-mg ELX/25-mg TEZ/37.5-mg IVA FDC tablet
- 150-mg IVA tablet
- 75-mg IVA tablet

All these tablets are authorised for this population and age group with the following dosing:

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

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

Study VX19-445-116, a Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF).

Study VX19-445-116 is a stand-alone study.

2.3.2. Clinical study

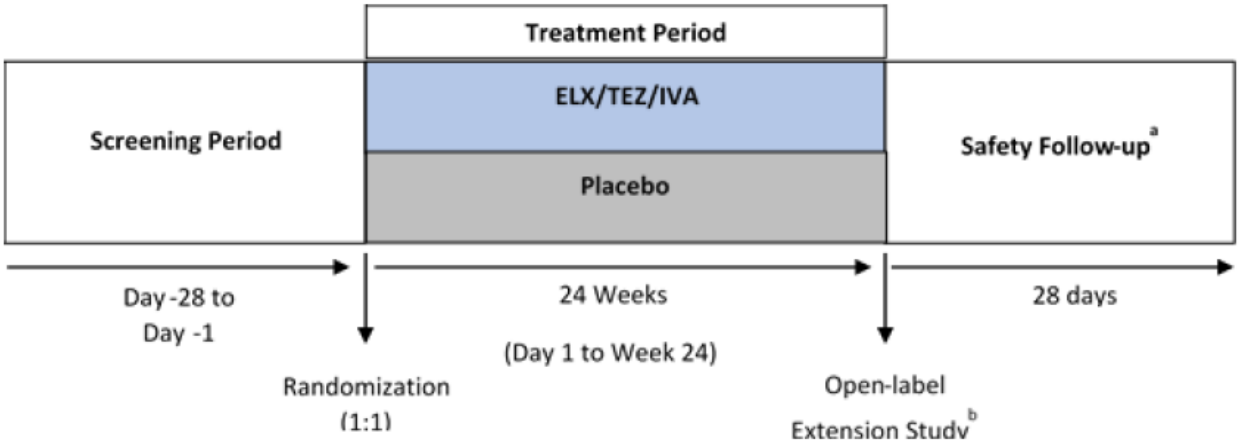
Clinical study number and title

Study VX19-445-116; a Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF).

Description

Methods

Study 116 was a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in CF subjects 6 through 11 years of age with F/MF genotypes.



Source: Study 116 CSR/Figure 9-1
ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
[a] The Safety Follow-up Visit was scheduled to occur 28 days (± 7 days) after the last dose.
[b] Subjects who completed the visits in the Treatment Period, regardless of whether they were on a treatment interruption, were offered the opportunity to enroll in an optional open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit was not required for subjects who completed the Week 24 Visit and enrolled in the open-label study within 28 days after the last dose of study drug.

Figure 1 Study 116 Study Design

CHMP comment

The duration of treatment was approximately 24 weeks. This is adequate to observe an effect on pulmonary function and sweat chloride.

Study participants

Table 1 Key Eligibility Criteria in Study 116

Inclusion Criteria	Exclusion Criteria
• Confirmed diagnosis of CF as determined by investigator • F/MF *CFTR* genotype • 6 through 11 years of age and ≥15 kg without shoes at the Screening Visit • Screening FEV_1 ≥70% (based on equations of the Global Lung Function Initiative[1]) and $LCI_{2.5}$ ≥7.5 at screening	• History of any illness or clinical condition that could confound the results of the study • Any protocol-defined laboratory values indicative of abnormal liver function or abnormal renal function • Any acute upper or lower respiratory infection, PEx, or changes in therapy for pulmonary disease within 28 days before first dose of study drug (Day 1) • Colonization with organisms associated with a more rapid decline in pulmonary status • An acute illness not related to CF within 14 days before the first dose of study drug (Day 1) • Pregnant or breast-feeding females

Sources: Study 116 CSR/Sections 9.3.1.1 and 9.3.1.2
CF: cystic fibrosis; F/MF: heterozygous for *F508del* and a minimal function mutation; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Other exclusion criteria were:

- Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL

- Total bilirubin ≥2 × upper limit of normal (ULN)
- Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
- Abnormal renal function defined as glomerular filtration rate ≤ 45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation)

CHMP comment

The inclusion criterion of ppFEV1 ≥70% is much higher than in other trials of the inclusion criterion of ppFEV1 ≥40%. This may have indicated that a less severe population could have been included. However, the inclusion of patients with $LCI_{2.5}$ ≥ 7.5 indicates that the small airways had to be impaired. Although the limitation to patients with ppFEV1 ≥ 70% is not fully understood, the in-and exclusion criteria are accepted.

Treatments

The dose of ELX/TEZ/IVA evaluated is 200 mg qd/100 mg qd/150 mg every q12h

Table 1 Treatment Period Groups and Dosages

Treatment Group Weight at Screening Visit	ELX Dosage	TEZ Dosage	IVA Dosage
ELX/TEZ/IVA			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
Placebo	0 mg	0 mg	0 mg

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

CHMP comment

The used dosing is identical to authorised dosing for this age group using identical weight classes.

Objective(s)

The Primary Objective is to evaluate the efficacy of ELX/TEZ/IVA in subjects 6 through 11 years of age with CF with F/MF genotypes.

The Secondary Objectives are to evaluate the PD of ELX/TEZ/IVA and the safety of ELX/TEZ/IVA.

Outcomes/endpoints

Primary efficacy endpoint

The absolute change in $LCI_{2.5}$ from baseline through Week 24.

Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry and ophthalmologic examinations (OEs)

Other Endpoints

- Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score from baseline through Week 24

CHMP comment

The endpoint are agreed, as they measure relevant aspects and goals for a treatment in CF. $LCI_{2.5}$ is a sensitive measurement for impairment in smaller airways, the part that is affected in the beginning of CF.

Sample size

Approximately 108 subjects were planned to be randomized (54 subjects in each treatment group).

The primary null hypothesis to be tested is that the mean absolute change in $LCI_{2.5}$ from baseline through Week 24 is the same for the 2 treatment groups, ELX/TEZ/IVA and placebo. The null hypothesis will be tested at a 2-sided significance level of 0.05.

Assuming a within-group SD of 1.5 and a treatment difference of -1.0 between ELX/TEZ/IVA and placebo, a sample size of 49 subjects completing the Treatment Period in each group for a total of 98 subjects will have approximately 90% power for the $LCI_{2.5}$ hypothesis testing, based on a 2-sided 2-sample t-test at a significance level of 0.05. Assuming a 10% dropout rate, approximately 108 subjects will be enrolled.

Randomisation and blinding (masking)

Approximately 108 subjects are planned to be randomized (1:1) to the ELX/TEZ/IVA group or the placebo group. Randomization will be stratified by $LCI_{2.5}$ determined at the Screening Visit (<10 versus ≥10) and weight at the Screening Visit (<30 kg versus ≥30 kg).

Randomization will occur before the first dose of study drug during the Treatment Period and may occur on either Day 1 or Day -1.

The study was performed blinded.

Statistical Methods

Efficacy and PD Analyses

Table 2 describes all efficacy and PD analyses based on the Full Analysis Set (FAS), with subjects grouped by their randomized treatment. Each continuous efficacy and PD endpoint was analysed using a mixed-effects model for repeated measures (MMRM) including treatment group, visit, and treatment-by-visit interaction as fixed effects. Baseline $LCI_{2.5}$ and weight at Screening (<30 versus ≥30 kg) were included in the model as covariates unless otherwise noted. In addition, descriptive summaries are provided for each efficacy and PD endpoint.

Table 2 Efficacy and PD Endpoints and Methods (FAS)

Endpoint	Method of Analysis
Primary Efficacy Endpoint	
Absolute change in $LCI_{2.5}$ from baseline through Week 24	Primary analysis • MMRM • LS Mean (95% CI) and *P* value through Week 24 for treatment difference • Line plot
Secondary Efficacy Endpoint	
Absolute change in SwCl from baseline through Week 24	• MMRM • LS Mean (95% CI) and nominal *P* value through Week 24 for treatment difference • Line plot
Other Efficacy Endpoints	
Absolute change in $ppFEV_1$ from baseline through Week 24	• MMRM • LS Mean (95% CI) and nominal *P* value through Week 24 for treatment difference • Line plot
Absolute change in CFQ-R RD score from baseline through Week 24	• MMRM • LS Mean (95% CI) and nominal *P* value through Week 24 for treatment difference • Line plot

CFQ-R: Cystic Fibrosis Questionnaire - Revised; FAS: Full Analysis Set; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; *P*: probability; PD: pharmacodynamic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride

Incomplete/missing data will not be imputed, unless specified otherwise.

Results

Participant flow

Approximately 108 subjects were planned to be randomized (54 subjects in each treatment group). The final number of subjects in each analysis set is provided in Table 3.

Table 3 Subject Disposition (All Subjects Set)

Disposition Reason	Placebo n (%)	ELX/TEZ/IVA n (%)	Total n (%)
All Subjects Set	61	60	121
Randomized	61	60	121
Safety Set	61	60	121
FAS	61	60	121
Randomized but not dosed	0	0	0
Completed treatment	61 (100.0)	59 (98.3)	120 (99.2)
Discontinued treatment	0	1 (1.7)	1 (0.8)
Reason for discontinuation of treatment			
AE	0	1 (1.7)	1 (0.8)
Completed study[a]	61 (100.0)	59 (98.3)	120 (99.2)
Discontinued study	0	1 (1.7)	1 (0.8)
Reason for discontinuation from study			
AE	0	1 (1.7)	1 (0.8)
Rollover to extension			
Yes	61 (100.0)	59 (98.3)	120 (99.2)
No	0	1 (1.7)	1 (0.8)

Source: Table 14.1.1

AE: adverse event; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

Note: All Subjects Set: all subjects who were randomized or received at least 1 dose of study drug; FAS: all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug; Safety Set: all subjects who received at least 1 dose of study drug.

[a] Completed study: completed Week 24 Visit, with Safety Follow-up, or rolled over to open-label extension study within 28 days after the last dose of study drug.

Recruitment

This study was conducted at 34 sites in Australia, Canada, Israel, Switzerland, UK, and the European Union (specifically, in Denmark, France, Germany, Netherlands, and Spain).

Study initiation: 19 June 2020 (date first eligible subject signed the informed consent form)

Study completion: 17 May 2021 (date last subject completed the last visit)

Conduct

There were no changes in conduct of the global study protocol and SAP

Safety measures were implemented to provide subjects the opportunity to continue participation in this study while ensuring their safety by minimizing the risk to COVID-19 exposure through travel. Remote monitoring visits, including remote source data verification, were permitted as allowed per local regulations.

An important protocol deviation (IPD) was defined as any protocol deviation that may have significantly affected the completeness, accuracy, or reliability of the study data or that may have significantly affected a subject's rights, safety, or well-being.

A total of 2 (1.7%) subjects had IPDs; for both subjects, the correct version of the ICF was not signed by subjects' parents.

CHMP comment

The two mentioned IPDs are not expected to have an impact on the results.

Baseline data

A total of 52 distinct F/MF genotypes were represented. Demographics are summarized in Table 4, and baseline characteristic data are summarized in Table 4.

Table 4 Subject Demographics (FAS)

Demographic	Placebo N = 61	ELX/TEZ/IVA N = 60	Total N = 121
Sex, n (%)			
Male	26 (42.6)	25 (41.7)	51 (42.1)
Female	35 (57.4)	35 (58.3)	70 (57.9)
Childbearing potential, n (%)			
Yes	17 (48.6)	19 (54.3)	36 (51.4)
No	18 (51.4)	16 (45.7)	34 (48.6)
Age at baseline (years)			
n	61	60	121
Mean (SD)	9.2 (1.7)	9.1 (1.8)	9.2 (1.7)
Median	9.1	8.9	9.0
Min, max	6.3, 11.7	6.1, 12.0	6.1, 12.0
Race, n (%)			
White	42 (68.9)	45 (75.0)	87 (71.9)
Black or African American	0	1 (1.7)	1 (0.8)
Asian	0	1 (1.7)	1 (0.8)
American Indian or Alaska Native	0	1 (1.7)	1 (0.8)
Not collected per local regulations	18 (29.5)	11 (18.3)	29 (24.0)
Other	1 (1.6)	0	1 (0.8)
Multiracial	0	1 (1.7)	1 (0.8)
Ethnicity, n (%)			
Hispanic or Latino	0	1 (1.7)	1 (0.8)
Not Hispanic or Latino	42 (68.9)	48 (80.0)	90 (74.4)
Not collected per local regulations	19 (31.1)	11 (18.3)	30 (24.8)

Source: Table 14.1.3

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

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period.

Table 5 Baseline Characteristics (FAS)

Characteristic	Placebo N = 61	ELX/TEZ/IVA N = 60	Total N = 121
Weight (kg)			
n	61	60	121
Mean (SD)	29.8 (8.6)	29.1 (7.6)	29.4 (8.1)
Median	27.3	27.1	27.2
Min, max	18.2, 59.8	16.2, 51.5	16.2, 59.8
Weight-for-age z-score			
n	61	60	121
Mean (SD)	-0.29 (0.96)	-0.27 (0.99)	-0.28 (0.97)
Median	-0.32	-0.29	-0.31
Min, max	-3.42, 1.95	-2.46, 1.52	-3.42, 1.95
Height (cm)			
n	61	60	121
Mean (SD)	134.6 (13.3)	132.3 (11.7)	133.5 (12.5)
Median	133.5	131.1	132.5
Min, max	99.7, 163.3	109.4, 159.4	99.7, 163.3
Height-for-age z-score			
n	61	60	121
Mean (SD)	0.01 (1.26)	-0.17 (1.02)	-0.08 (1.14)
Median	0.14	-0.16	0.01
Min, max	-6.36, 2.19	-2.55, 1.90	-6.36, 2.19
BMI (kg/m^2)			
n	61	60	121
Mean (SD)	16.11 (2.32)	16.33 (1.84)	16.21 (2.09)
Median	15.65	15.87	15.83
Min, max	13.04, 27.86	13.54, 21.91	13.04, 27.86
BMI-for-age z-score			
n	61	60	121
Mean (SD)	-0.39 (0.92)	-0.17 (0.85)	-0.28 (0.89)
Median	-0.33	-0.16	-0.25
Min, max	-2.57, 2.14	-1.88, 1.59	-2.57, 2.14
$LCI_{2.5}$ at Screening, n (%)			
<10	35 (57.4)	34 (56.7)	69 (57.0)
≥10	26 (42.6)	26 (43.3)	52 (43.0)
Weight (kg) at Screening, n (%)			
<30	38 (62.3)	39 (65.0)	77 (63.6)
≥30	23 (37.7)	21 (35.0)	44 (36.4)
$LCI_{2.5}$ at baseline			
n	61	60	121
Mean (SD)	9.75 (1.95)	10.26 (2.22)	10.01 (2.09)
Median	9.14	9.71	9.46
Min, max	6.91, 15.75	7.13, 18.36	6.91, 18.36
Sweat chloride (mmol/L) at baseline			
n	61	60	121
Mean (SD)	102.6 (8.6)	102.8 (10.0)	102.7 (9.3)
Median	104.0	103.5	104.0
Min, max	83.5, 123.0	77.0, 123.5	77.0, 123.5

$ppFEV_1$ category at baseline, n (%)			
<70	10 (16.4)	4 (6.7)	14 (11.6)
≥70 to ≤90	23 (37.7)	20 (33.3)	43 (35.5)
>90	28 (45.9)	36 (60.0)	64 (52.9)
$ppFEV_1$ at baseline			
n	61	60	121
Mean (SD)	87.2 (15.8)	91.4 (13.8)	89.3 (15.0)
Median	89.6	93.0	91.7
Min, max	55.8, 119.6	44.6, 121.8	44.6, 121.8
CFQ-R respiratory domain score (child's version) at baseline			
n	61	60	121
Mean (SD)	82.7 (14.1)	85.7 (11.7)	84.2 (13.0)
Median	83.3	83.3	83.3
Min, max	50.0, 100.0	50.0, 100.0	50.0, 100.0
Prior use of dornase alfa[a], n (%)			
Yes	41 (67.2)	42 (70.0)	83 (68.6)
No	20 (32.8)	18 (30.0)	38 (31.4)
Prior use of azithromycin[a], n (%)			
Yes	9 (14.8)	11 (18.3)	20 (16.5)
No	52 (85.2)	49 (81.7)	101 (83.5)
Prior use of inhaled antibiotic[a], n (%)			
Yes	8 (13.1)	15 (25.0)	23 (19.0)
No	53 (86.9)	45 (75.0)	98 (81.0)
Prior use of any bronchodilator[a], n (%)			
Yes	46 (75.4)	38 (63.3)	84 (69.4)
No	15 (24.6)	22 (36.7)	37 (30.6)
Prior use of any inhaled bronchodilator[a], n (%)			
Yes	46 (75.4)	38 (63.3)	84 (69.4)
No	15 (24.6)	22 (36.7)	37 (30.6)
Prior use of any inhaled hypertonic saline[a], n (%)			
Yes	46 (75.4)	46 (76.7)	92 (76.0)
No	15 (24.6)	14 (23.3)	29 (24.0)
Prior use of any inhaled corticosteroids[a], n (%)			
Yes	18 (29.5)	15 (25.0)	33 (27.3)
No	43 (70.5)	45 (75.0)	88 (72.7)

Source: Table 14.1.4

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; N: total sample size; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period.

[a] Included medications administered during the 56 days before the first dose of study drug in the Treatment Period.

***CHMP* comments**

A total of 14 subjects had ppFEV1 < 70%, thus lower than the inclusion criterion of ppFEV1 ≥ 70%.

However, these baseline values LCI2.5 < 7.5 and/or ppFEV1< 70% were post-screening values. Therefore, the subjects were still considered to have met eligibility criteria.

Prior and Concomitant Medications

Table 6 summarizes concomitant medications received by at least 20% of subjects overall by PN. The most common concomitant medications were typically used for the management of CF.

Table 6 Concomitant Medications Received by At Least 20% of Subjects Overall by PN (FAS)

Preferred Name	Placebo N = 61 n (%)	ELX/TEZ/IVA N = 60 n (%)	Total N = 121 n (%)
Subjects with any concomitant medication	61 (100.0)	60 (100.0)	121 (100.0)
Pancreatin	53 (86.9)	52 (86.7)	105 (86.8)
Sodium chloride	54 (88.5)	51 (85.0)	105 (86.8)
Dornase alfa	40 (65.6)	43 (71.7)	83 (68.6)
Salbutamol	45 (73.8)	36 (60.0)	81 (66.9)
Ursodeoxycholic acid	15 (24.6)	21 (35.0)	36 (29.8)
Paracetamol	18 (29.5)	12 (20.0)	30 (24.8)
Omeprazole	16 (26.2)	12 (20.0)	28 (23.1)
Vitamin D NOS	17 (27.9)	11 (18.3)	28 (23.1)
Retinol	14 (23.0)	11 (18.3)	25 (20.7)

Source: Table 14.1.6.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NOS: not otherwise specified; PN: Preferred Name; TE: treatment-emergent; TEZ: tezacaftor; WHO-DD: World Health Organization-Drug Dictionary

Notes: Medications were coded using WHO-DD, version March 2021 format B3. PNs were sorted in descending order of frequency of the Total column. A subject with multiple medications within a category was counted only once within that category.

Number analysed

Details of subject disposition are summarized in Table 7

.

Table 7 Subject Disposition (All Subjects Set)

Disposition Reason	Placebo n (%)	ELX/TEZ/IVA n (%)	Total n (%)
All Subjects Set	61	60	121
Randomized	61	60	121
Safety Set	61	60	121
FAS	61	60	121
Randomized but not dosed	0	0	0
Completed treatment	61 (100.0)	59 (98.3)	120 (99.2)
Discontinued treatment	0	1 (1.7)	1 (0.8)
Reason for discontinuation of treatment			
AE	0	1 (1.7)	1 (0.8)
Completed study[a]	61 (100.0)	59 (98.3)	120 (99.2)
Discontinued study	0	1 (1.7)	1 (0.8)
Reason for discontinuation from study			
AE	0	1 (1.7)	1 (0.8)
Rollover to extension			
Yes	61 (100.0)	59 (98.3)	120 (99.2)
No	0	1 (1.7)	1 (0.8)

Source: Table 14.1.1

AE: adverse event; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

Note: All Subjects Set: all subjects who were randomized or received at least 1 dose of study drug; FAS: all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug; Safety Set: all subjects who received at least 1 dose of study drug.

[a] Completed study: completed Week 24 Visit, with Safety Follow-up, or rolled over to open-label extension study within 28 days after the last dose of study drug.

Efficacy results LCI2.5

Primary endpoint

Treatment with ELX/TEZ/IVA over 24 weeks in CF subjects 6 through 11 years of age with F/MF genotypes resulted in a statistically significant, improvement in the primary efficacy endpoint.

The LS mean treatment difference for the ELX/TEZ/IVA group versus placebo for the absolute change in LCI2.5 from baseline through Week 24 was -2.26 (95% CI: -2.71, -1.81; P<0.0001).

The analysis of absolute change in LCI2.5 from baseline through Week 24 is presented in Table 8 and Figure 2.

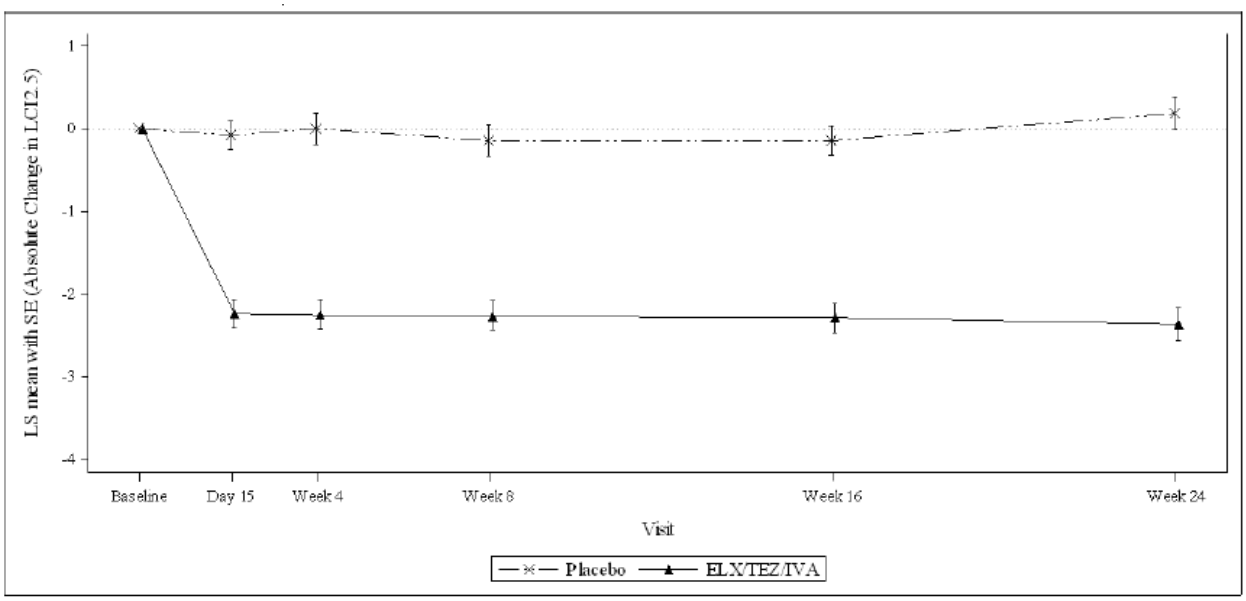
Table 8 MMRM Analysis of Absolute Change From Baseline in $LCI_{2.5}$ Through Week 24 (FAS)

	Placebo N = 61	ELX/TEZ/IVA N = 60
Baseline		
n	61	60
Mean (SD)	9.75 (1.95)	10.26 (2.22)
Absolute change through Week 24		
n	61	60
LS mean (SE)	-0.02 (0.16)	-2.29 (0.16)
95% CI of LS mean	(-0.34, 0.29)	(-2.60, -1.97)
P value within treatment	0.8859	<0.0001
LS mean difference (SE)	--	-2.26 (0.23)
95% CI of LS mean	--	(-2.71, -1.81)
P value versus placebo	--	<0.0001

Source: Table 14.2.1.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; TEZ: tezacaftor

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 24, with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline $LCI_{2.5}$ and weight at Screening (<30 versus ≥30 kg) 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 24.



Source: Figure 14.2.1.1

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; TEZ: tezacaftor

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, with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline $LCI_{2.5}$ and weight at Screening (<30 versus ≥30 kg) 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 Baseline in $LCI_{2.5}$ by Visit (FAS)

***CHMP* comments**

The LS mean absolute change in LCI2.5 was measured from baseline through Week 24. However, the use of absolute change from baseline at week 24, would have been preferred.

The additional analysis of the absolute change in LCI2.5 at Day 15 showed that the results are consistent with the primary analysis of absolute change in LCI2.5 from baseline through Week 24 (LS mean treatment difference of -2.26 [95% CI: -2.71, -1.81] for the ELX/TEZ/IVA group versus placebo). In table 14.2.1.6.5 also the change from baseline at week 24 were provided: -2.76 (-3.36, -2.16). Based on this information, it is considered the absolute change in LCI2.5 from baseline at Week 24 is also consistent (or a slightly better) than absolute change in LCI2.5 from baseline through Week 24 (Figure 2).

The robustness of the data was confirmed by sensitivity analyses that account for the missing data.

Secondary endpoints

Results for absolute change from baseline through Week 24 for all efficacy endpoints were as follows:

- The LS mean treatment difference for the ELX/TEZ/IVA group versus placebo for the absolute change in SwCl from baseline through Week 24 was -51.2 mmol/L (95% CI: -55.3, -47.1; nominal P<0.0001).

- The LS mean treatment difference for the ELX/TEZ/IVA group versus placebo for the absolute change in ppFEV1 from baseline through Week 24 was 11.0 percentage points (95% CI: 6.9, 15.1; nominal P<0.0001).
- The LS mean treatment difference for the ELX/TEZ/IVA group versus placebo for the absolute change in CFQ-R RD score from baseline through Week 24 was 5.5 points (95% CI: 1.0, 10.0; nominal P = 0.0174).

***CHMP* comments**

For LCI2.5, sweat chloride, CFQ-R, ppFEV1, missing data patterns over the full follow up period were provided. These missing data was mostly at week 24 (e.g. for LCI2.5 8.2% missing in placebo vs 16.7% in Kaftrio). Most common reason was 'not meeting criteria', and only in very few cases due AE, non-compliance, death, physician decision, or subject refusal or prohibited medication. Therefore, missing data can be considered not related to underlying outcome as the applicant explained that 'not meeting criteria' was not related to the underlying outcome. For LCI2.5, the primary endpoint, a jump-to-reference missing data imputation was performed as sensitivity analysis. The estimate (95%-CI) was -2.32 (-2.76, -1.88) for the jump-to-reference imputation compared to 2.26 (-2.71, -1.81) in the primary analysis. Thus, efficacy results are considered robust.

Safety results

Exposure

A total of 121 subjects received at least 1 dose of study drug in the Treatment Period. The mean exposure was 23.7 weeks in the ELX/TEZ/IVA group and 24.0 weeks in the placebo group.

Table 9 Summary of Exposure (Safety Set)

	Placebo N = 61	ELX/TEZ/IVA N = 60
Total exposure (patient weeks)	1466.9	1421.7
Exposure duration (weeks)		
n	61	60
Mean (SD)	24.0 (0.4)	23.7 (3.0)
Median	24.0	24.0
Min, max	23.1, 25.0	1.0, 25.0
Exposure duration by interval, n (%)		
≤15 days	0	1 (1.7)
>15 days to ≤4 weeks	0	0
>4 to ≤8 weeks	0	0
>8 to ≤12 weeks	0	0
>12 to ≤16 weeks	0	0
>16 to ≤20 weeks	0	0
>20 to ≤24 weeks	37 (60.7)	34 (56.7)
>24 weeks	24 (39.3)	25 (41.7)

Source: Table 14.1.7
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects. Duration of study drug exposure (weeks) = (last dose date – first dose date + 1)/7, regardless of study drug interruption.

Adverse events

The incidence of subjects with at least 1 AE was 80.0% in the ELX/TEZ/IVA group and 93.4% in the placebo group. The majority of subjects had AEs that were mild or moderate in severity; 2 (3.3%) subjects in the ELX/TEZ/IVA group and 2 (3.3%) subjects in the placebo group had severe AEs. Serious AEs (SAEs) occurred in 4 (6.7%) subjects in the ELX/TEZ/IVA group and 9 (14.8%) subjects in the placebo group. In the ELX/TEZ/IVA group, 1 (1.7%) subject discontinued study drug due to an AE and 7 (11.7%) subjects interrupted study drug due to AEs. No subjects in the placebo group discontinued or interrupted study drug. There were no life-threatening AEs and no deaths.

Table 10 Overview of Adverse Events (Safety Set)

	Placebo N = 61 n (%)	ELX/TEZ/IVA N = 60 n (%)	Total N = 121 n (%)
Number of AEs (total)	335	212	547
Subjects with any AEs	57 (93.4)	48 (80.0)	105 (86.8)
Subjects with AEs by strongest relationship			
Not related	17 (27.9)	12 (20.0)	29 (24.0)
Unlikely related	17 (27.9)	10 (16.7)	27 (22.3)
Possibly related	21 (34.4)	24 (40.0)	45 (37.2)
Related	2 (3.3)	2 (3.3)	4 (3.3)
Subjects with AEs by maximum severity			
Grade 1/Mild	26 (42.6)	30 (50.0)	56 (46.3)
Grade 2/Moderate	29 (47.5)	16 (26.7)	45 (37.2)
Grade 3/Severe	2 (3.3)	2 (3.3)	4 (3.3)
Grade 4/Life-threatening	0	0	0
Subjects with AEs leading to treatment discontinuation	0	1 (1.7)	1 (0.8)
Subjects with AEs leading to treatment interruption	0	7 (11.7)	7 (5.8)
Subjects with Grade 3/4 AEs	2 (3.3)	2 (3.3)	4 (3.3)
Subjects with related AEs	23 (37.7)	26 (43.3)	49 (40.5)
Subjects with SAEs	9 (14.8)	4 (6.7)	13 (10.7)
Subjects with related SAEs	1 (1.6)	1 (1.7)	2 (1.7)
Subjects with AEs leading to death	0	0	0

Source: Table 14.3.1.1

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

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. An AE with relationship missing is counted as related. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. Subjects with Grade 3/4 AEs included the "Severe" and "Life Threatening" categories. If a subject only had 1 event which had missing severity, then the subject was summarized in the "Missing" category.

Common adverse events

AEs that occurred in ≥ 5% of subjects in any treatment group are summarized by PT in Table 11.

Overall, the AEs were mostly consistent with common manifestations or complications of CF disease in CF subjects 6 through 11 years of age or with the established safety profile of ELX/TEZ/IVA.

Table 11 AEs Occurring in At Least 5% of Subjects in Any Treatment Group (Safety Set)

Preferred Term	Placebo N = 61 n (%)	ELX/TEZ/IVA N = 60 n (%)
Subjects with any AEs	57 (93.4)	48 (80.0)
Headache	12 (19.7)	18 (30.0)
Cough	26 (42.6)	14 (23.3)
Nasopharyngitis	9 (14.8)	7 (11.7)
Productive cough	6 (9.8)	7 (11.7)
Rhinorrhoea	7 (11.5)	7 (11.7)
Rash	3 (4.9)	6 (10.0)
Abdominal pain	17 (27.9)	5 (8.3)
Alanine aminotransferase increased	3 (4.9)	5 (8.3)
Abdominal pain upper	5 (8.2)	4 (6.7)
Diarrhoea	6 (9.8)	4 (6.7)
Pruritus	0	4 (6.7)
Staphylococcus test positive	1 (1.6)	4 (6.7)
Aspartate aminotransferase increased	1 (1.6)	3 (5.0)
Nasal congestion	3 (4.9)	3 (5.0)
Oropharyngeal pain	12 (19.7)	3 (5.0)
Rhinitis	5 (8.2)	3 (5.0)
Steatorrhoea	0	3 (5.0)
Upper respiratory tract infection	5 (8.2)	3 (5.0)
Vomiting	4 (6.6)	3 (5.0)
Arthralgia	4 (6.6)	1 (1.7)
Bacterial test positive	4 (6.6)	1 (1.7)
Infective PEx of CF	16 (26.2)	1 (1.7)
Nausea	5 (8.2)	1 (1.7)
Fatigue	5 (8.2)	0
Forced expiratory volume decreased	4 (6.6)	0
Nasal polyps	5 (8.2)	0

Source: Table 14.3.1.3

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

Severity of Adverse Events

The majority of subjects overall had AEs that were mild (46.3%) or moderate (37.2%) in severity.

In the ELX/TEZ/IVA group, 2 (3.3%) subjects had severe AEs (both subjects had AEs of rash) and no subjects had life-threatening AEs. In the placebo group, 2 (3.3%) subjects had severe AEs (1 subject had an AE of nasal polyps and 1 subject had AEs of distal intestinal obstruction syndrome) and no subjects had life-threatening AEs.

Relationship of Adverse Events

Two (3.3%) subjects in the ELX/TEZ/IVA group and 2 (3.3%) subjects in the placebo group had an AE assessed by the investigator as related; 24 (40.0%) subjects in the ELX/TEZ/IVA group and 21

(34.4%) subjects in the placebo group had an AE assessed by the investigator as possibly related. (Table 12)

Table 12 Related AEs Occurring in ≥5 Subjects in Any Treatment Group (Safety Set)

System Organ Class Preferred Term	Placebo N = 61 n (%)	ELX/TEZ/IVA N = 60 n (%)
Subjects with any related AEs	23 (37.7)	26 (43.3)
Skin and subcutaneous tissue disorders	1 (1.6)	11 (18.3)
Rash	0	5 (8.3)
Respiratory, thoracic and mediastinal disorders	7 (11.5)	10 (16.7)
Cough	6 (9.8)	6 (10.0)
Gastrointestinal disorders	12 (19.7)	7 (11.7)
Abdominal pain	7 (11.5)	2 (3.3)
Nervous system disorders	6 (9.8)	6 (10.0)
Headache	6 (9.8)	4 (6.7)

Source: Table 14.3.1.6

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class; TEZ: tezacaftor

Notes: AEs were coded using MedDRA version 24.0. A subject with multiple events within a category was counted only once in that category. A subject with multiple events within a PT was counted only once in that PT. Table was sorted in descending order of frequency of the ELX/TEZ/IVA column by SOC, and by PT within each SOC. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing are counted.

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

There were no AEs leading to death.

Four (6.7%) subjects in the ELX/TEZ/IVA group and 9 (14.8%) subjects in the placebo group had at least 1 SAE . No SAE occurred in more than 1 subject in the ELX/TEZ/IVA group. Three (4.9%) subjects in the placebo group had an SAE of infective PEx of CF.

The majority of SAEs were assessed by the investigator as unlikely related or not related to study drug. Related (combined related or possibly related) SAEs are presented in Table 13.

Table 13 Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term Safety Set

System Organ Class Preferred Term	Placebo N = 61 n (%)	ELX/TEZ/IVA N = 60 n (%)
Subjects with any serious TEAEs	9 (14.8)	4 (6.7)
Congenital, familial and genetic disorders	0	1 (1.7)
Phimosis	0	1 (1.7)
Infections and infestations	4 (6.6)	1 (1.7)
Varicella zoster virus infection	0	1 (1.7)
Infective pulmonary exacerbation of cystic fibrosis	3 (4.9)	0
Pneumonia pseudomonal	1 (1.6)	0
Investigations	0	1 (1.7)
Bacterial test positive	0	1 (1.7)
Skin and subcutaneous tissue disorders	0	1 (1.7)
Rash	0	1 (1.7)
Blood and lymphatic system disorders	1 (1.6)	0
Lymphadenitis	1 (1.6)	0
Gastrointestinal disorders	2 (3.3)	0
Distal intestinal obstruction syndrome	1 (1.6)	0
Intussusception	1 (1.6)	0
General disorders and administration site conditions	1 (1.6)	0
General physical health deterioration	1 (1.6)	0
Respiratory, thoracic and mediastinal disorders	1 (1.6)	0
Nasal polyps	1 (1.6)	0
Subjects with any related serious TEAEs	1 (1.6)	1 (1.7)
Skin and subcutaneous tissue disorders	0	1 (1.7)
Rash	0	1 (1.7)
Gastrointestinal disorders	1 (1.6)	0
Distal intestinal obstruction syndrome	1 (1.6)	0

- MedDRA version 24.0.
- TEAE: Treatment-emergent adverse event.
- A subject with multiple events within a category is counted only once in that category. A subject with multiple events within a Preferred Term is counted only once in that Preferred Term.
- Table is sorted in descending order of ELX/TEZ/IVA by SOC, and by PT within each SOC.
- When summarizing number of subjects with related serious TEAEs, TEAEs with relationship of related, possibly related, and missing are counted.

Study drug discontinuation

One (1.7%) subject in the ELX/TEZ/IVA group had an AE of rash that led to study drug discontinuation. The event was assessed as severe and possibly related to study drug. Study drug was withdrawn, and the event resolved. No subjects in the placebo group discontinued study drug.

Adverse Events That Led to Interruption of Study Drug

Seven (11.7%) subjects in the ELX/TEZ/IVA group interrupted study drug due to an AE. AEs that led to treatment interruption that occurred in ≥2 subjects were ALT increased and AST increased. No subjects in the placebo group had AEs that led to treatment interruption.

Table 14 Treatment-emergent Adverse Events Leading to Treatment Interruption by System Organ Class and Preferred Term Safety Set

System Organ Class Preferred Term	Placebo N = 61 n (%)	ELX/TEZ/IVA N = 60 n (%)
Subjects with TEAEs leading to treatment interruption	0	7 (11.7)
Investigations	0	4 (6.7)
Alanine aminotransferase increased	0	4 (6.7)
Aspartate aminotransferase increased	0	2 (3.3)
Gamma-glutamyltransferase increased	0	1 (1.7)
Skin and subcutaneous tissue disorders	0	2 (3.3)
Rash	0	1 (1.7)
Rash maculo-papular	0	1 (1.7)
Gastrointestinal disorders	0	1 (1.7)
Nausea	0	1 (1.7)

- MedDRA version 24.0.
- TEAE: Treatment-emergent adverse event.
- A subject with multiple events within a category is counted only once in that category. A subject with multiple events within a Preferred Term is counted only once in that Preferred Term.
- Table is sorted in descending order of ELX/TEZ/IVA by SOC, and by PT within each SOC.

Adverse Events of Special Interest

AESI were defined as AEs of elevated transaminases and AEs of rash.

Six (10.0%) subjects in the ELX/TEZ/IVA group and 3 (4.9%) subjects in the placebo group had at least 1 elevated transaminase event. All events were mild or moderate in severity, and none were serious. Four (6.7%) subjects in the ELX/TEZ/IVA group interrupted study drug due to elevated transaminase events. No subjects discontinued study drug due to elevated transaminase events.

Table 15 Summary of Elevated Transaminase Events (Safety Set)

	Placebo N = 61	ELX/TEZ/IVA N = 60
Subjects with any elevated transaminase events, n (%)	3 (4.9)	6 (10.0)
ALT increased	3 (4.9)	5 (8.3)
AST increased	1 (1.6)	3 (5.0)
Subjects with elevated transaminase events by maximum severity, n (%)		
Grade 1/Mild	2 (3.3)	3 (5.0)
Grade 2/Moderate	1 (1.6)	3 (5.0)
Grade 3/Severe	0	0
Grade 4/Life-threatening	0	0
Subjects with elevated transaminase events leading to treatment discontinuation, n (%)	0	0
Subjects with serious elevated transaminase events, n (%)	0	0
Subjects with related serious elevated transaminase events[a], n (%)	0	0
Subjects with elevated transaminase events leading to treatment interruption, n (%)	0	4 (6.7)
Subjects with elevated transaminase events leading to death, n (%)	0	0
Time-to-onset of first elevated transaminase event (days)[b]		
Subjects with elevated transaminase event with complete start date	3	6
Mean (SD)	62.0 (91.8)	66.0 (51.1)
Median	11.0	56.5
Min, max	7, 168	15, 140
Duration of elevated transaminase events (days)[b]		
Number of events	6	12
Number of events with duration	5	11
Mean (SD)	10.4 (8.5)	25.7 (15.1)
Median	7.0	23.0
Min, max	2, 20	4, 58

Source: Table 14.3.2.8

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

Notes: Events were coded using MedDRA version 24.0. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number of subjects with events, a subject with multiple events within a category is counted only once in that category. A subject with multiple events within a PT is counted only once in that PT. PTs were sorted by alphabetical order.

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

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

Eight (13.3%) subjects in the ELX/TEZ/IVA group and 3 (4.9%) subjects in the placebo group had a least 1 rash event. The majority of events were mild or moderate in severity. One (1.7 %) subject in the ELX/TEZ/IVA group had a rash event that led to treatment discontinuation. Two (3.3%) subjects in the ELX/TEZ/IVA group interrupted study drug due to rash events; both subjects successfully resumed study drug without recurrence of rash. No subjects in the placebo group had rash events that led to treatment discontinuation or interruption.

Clinical Laboratory Evaluation

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

Mean concentrations of LFT parameters were variable over time in both treatment groups. There were no trends in ALT, AST, ALP, or GGT for either group.

ALT or AST >3, >5, and >8 × ULN occurred in 8 (13.6%), 3 (5.1%), and 1 (1.7%) subject(s) in the ELX/TEZ/IVA group, compared to 3 (4.9%), 1 (1.6%), and 0 subject(s) in the placebo group. No subjects had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN.

Table 16 Threshold Analysis of LFT Chemistry Parameters During the TE Period (Safety Set) (shortened by assessor)

Parameter Subjects With Non-missing Post-baseline Data Post-baseline Threshold Analysis Criteria, n (%)	Placebo N = 61	ELX/TEZ/IVA N = 60
ALT (U/L)		
Total, N1	61	59
>3 × ULN	3 (4.9)	8 (13.6)
>5 × ULN	1 (1.6)	3 (5.1)
>8 × ULN	0	1 (1.7)
AST (U/L)		
Total, N1	61	59
>3 × ULN	0	1 (1.7)
>5 × ULN	0	0
>8 × ULN	0	0
ALT (U/L) or AST (U/L)		
Total, N1	61	59
(ALT>3 × ULN) or (AST>3 × ULN)	3 (4.9)	8 (13.6)
(ALT>5 × ULN) or (AST>5 × ULN)	1 (1.6)	3 (5.1)
(ALT>8 × ULN) or (AST>8 × ULN)	0	1 (1.7)
Total bilirubin (µmol/L)		
Total, N1	61	59
(ALT or AST) and TBILI		
Total, N1	61	59
(ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN	0	0

Source: Table 14.3.4.2

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; GGT: gamma-glutamyl transferase; IVA: ivacaftor; LFT: liver function test; n: number of subjects in the post-baseline category.; N: total sample size; N1: number of subjects with at least 1 non-missing measurement during the TE Period; TBILI: total bilirubin; TE: treatment-emergent; TEZ: tezacaftor; ULN: upper limit of normal

Notes: 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.

2.3.3. Discussion on clinical aspects

In the EU, Kaftrio is approved as a combination regimen with ivacaftor for the treatment of patients with CF in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Design and conduct

Study VX19-445-116 is a Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF).

The investigated dose of ELX/TEZ/IVA is identical with the dose authorized for the age group and weight classes.

Male and female CF subjects 6 through 11 years of age with F/MF genotypes were included with screening FEV_1 ≥70% and $LCI_{2.5}$ ≥7.5. The inclusion criterion of ppFEV1 ≥ 70% may have indicated that a less severe population could have been included. However, the inclusion of patients with $LCI_{2.5}$ ≥ 7.5 indicates that the small airways had to be impaired. Although the limitation to patients with ppFEV1 ≥ 70% is not fully understood, the in-and exclusion criteria are accepted.

For efficacy evaluation, Multiple-breath washout, spirometry, Cystic Fibrosis Questionnaire-Revised (CFQ-R), and sweat chloride (SwCl) were assessed. These are all relevant parameters. The $LCI_{2.5}$ can measure changes in the small airways, while the ppFEV1 is more associated with large airways. In CF, the small airways are earlier affected than the large airways. Therefore, the use of the $LCI_{2.5}$ as a measurement of efficacy is acceptable, given the usually well-preserved lung function in children. However, the $LCI_{2.5}$ at week 24 would have been preferred instead of through week 24. Evaluation of BMI-z-score would also have been appreciated. Nevertheless, the chosen endpoints are sufficient. Safety parameters were the usual measurements.

All efficacy and PD analyses based on the Full Analysis Set (FAS). Each continuous efficacy and PD endpoint was analysed using a mixed-effects model for repeated measures (MMRM) including treatment group, visit, and treatment-by-visit interaction as fixed effects. Baseline $LCI_{2.5}$ and weight at Screening (<30 versus ≥30 kg) were included in the model as covariates unless otherwise noted. Statistics were considered adequate.

Demographics and patient characteristics

A total of 52 distinct F/MF genotypes were represented. More female (57.9% were included compared with male (42.1%). The demographics and baseline characteristics were generally well balanced. The mean (SD) weight at baseline was 29.4 (8.1) kg, and the mean (SD) weight z-score at baseline was -0.28 (0.97), indicating that baseline weights were below average for subjects' age and sex. The mean (SD) baseline BMI z-score was -0.28 (0.89) and mean (SD) baseline height z-score was -0.08 (1.14). Mean (SD) baseline $LCI_{2.5}$ was 10.01 (2.09) indicating that the small airways were already affected. Mean baseline ppFEV1 was 89.3% indicating that FEV1 was still well preserved, but the range (44.6-121.8%) indicated that subjects could already have impaired FEV1. A total of 14 subjects had baseline ppFEV1 < 70%, thus lower than the inclusion criterion of ppFEV1 ≥ 70%. This could be explained that these baseline values $LCI_{2.5}$ < 7.5 and/or of ppFEV1< 70% were post-screening values. Although it is acknowledged that there are usually some differences between screening and baseline values, the number of patients that were eligible but had lower values at baseline is considered rather high, Nevertheless, it is agreed that the subjects were eligible.

Results

The LS mean treatment difference for the ELX/TEZ/IVA group versus placebo for the absolute change in $LCI_{2.5}$ from baseline through Week 24 was -2.26 (95% CI: -2.71, -1.81; P<0.0001). The minimal clinically important difference (MCID) for the $LCI_{2.5}$ is not known. Therefore, an effect larger than the natural variability might be regarded as clinically relevant. The natural variability for the $LCI_{2.5}$ is ± 0.9 unit or 15 % of baseline[1]. Based on these recommendation and previously accepted margin of 1 unit, the study can be considered to have met the primary objective. Additional results at D15 and at Week 24 were consistent with the results of absolute change in $LCI_{2.5}$ from baseline through Week 24.

As for the secondary endpoints, all endpoints showed a statistically significant difference for the ELX/TEZ/IVA group versus placebo. The results of all secondary endpoints can be considered supportive for the primary analyses as they also met the clinically relevant changes.

[1] Oude Engberink et al. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. Eur Respir J 2017; 50: 1700433 https://doi.org/10.1183/13993003.00433-2017

Sweat chloride is a biomarker of CFTR function. The absolute change from baseline through Week 24 was for SwCl -51.2 mmol/L (95% CI: -55.3, -47.1; nominal P<0.0001), for ppFEV1 from baseline through Week 24 was 11.0 percentage points (95% CI: 6.9, 15.1; nominal P<0.0001) and for CFQ-R RD score from baseline through Week 24 was 5.5 points (95% CI: 1.0, 10.0; nominal P = 0.0174). For all endpoints it can be concluded that the differences are clinically relevant. A reduction SwCl ≥ 10-15 mmol/l has been accepted as minimum. In the authorisation study in children aged 6 through 12 years of TEZ/ELX/IVA a decrease of -60.9 mmol/L from baseline through week 24 has been observed. Preservation of lung function is a main goal in the treatment of cystic fibrosis. The less impaired lung function in this younger population may be of influence for this difference. Therefore, the increase in absolute change in ppFEV1 from baseline through Week 24 of 11.0% is considered an important improvement and the relevance is beyond doubt.
The CFQ-R indicates is used to indicate a patient benefit in daily life. An increase of > 4 points indicates that the patient can perceive a change in daily life, expressed as minimal clinical important difference (MCID). The LS mean absolute change from baseline through week 24 in CFQ-R respiratory domain score was 5.5 points. This was above the minimal clinically important difference (MCID) of 4 points.

For each of the endpoints, not all participants had data available at all timepoints. The current analysis methods assume that the data are missing at random. Missing data was largely at week 24 (e.g. for $LCI_{2.5}$ 8.2% missing in placebo vs 16.7% in Kaftrio). Most common reason was 'not meeting criteria', and only in very few cases due AE, non-compliance, death, physician decision, or subject refusal or prohibited medication. Therefore, missing data can be considered not related to underlying outcome. For $LCI_{2.5}$, the primary endpoint, also a jump-to-reference missing data imputation was performed and this confirmed the primary analysis. Thus, efficacy results are considered robust.

Safety

All 121 subjects received at least 1 dose of study drug in the treatment period with a mean exposure of 23.7 weeks in the ELX/TEZ/IVA group and 24.0 weeks in the placebo group.

The incidence of subjects with at least 1 AE was 80.0% in the ELX/TEZ/IVA group and 93.4% in the placebo group. The most common AEs (occurring in ≥ 10% of subjects in either treatment arm) were headache, cough, nasopharyngitis, productive cough, rhinorrhoea, rash, abdominal pain, oropharyngeal pain, and infective PEx of CF. Relevant differences in incidence of AEs that were more frequent in ELX/TEZ/IVA compared with placebo (n (%) were observed for rash (6 (10.0) vs 3 (4.9)), alanine aminotransferase increased (5 (8.3) vs 3 (4.9)), pruritus (4 (6.7) vs 0), staphylococcus test positive (4 (6.7) vs 1 (1.6)) and aspartate aminotransferase increased (3 (5.0) vs 1 (1.6)). An important difference in favour of ELX/TEZ/IVA was the relevant difference in infective PEx of CF being much higher in the placebo group 16 (26.2) compared to 1 (1.7) in the ELX/TEZ/IVA group.
Overall, the AEs were mostly consistent with common manifestations or complications of CF disease in CF subjects 6 through 11 years of ageand the differences are consistent with the established safety profile of ELX/TEZ/IVA.

The majority of subjects had AEs that were mild or moderate in severity, while only 2 (3.3%) subjects in the ELX/TEZ/IVA group and 2 (3.3%) subjects in the placebo group had severe AEs. There were no life-threatening AEs and no deaths.

Serious adverse event (SAE) occurred in 4 (6.7%) subjects in the ELX/TEZ/IVA group and 9 (14.8%) subjects in the placebo group. No SAE occurred in more than 1 subject each in the ELX/TEZ/IVA group. Three (4.9%) subjects in the placebo group had an SAE of infective pulmonary exacerbation (PEx) of CF. Overall, the observed SAEs were consistent with common manifestations or complications of CF disease in CF children 6 through 11 years of age or with the established safety profile of ELX/TEZ/IVA.

In the ELX/TEZ/IVA group, 1 (1.7%) subject discontinued study drug due to an AE (rash), and 7 (11.7%) subjects interrupted study drug due to AEs, mostly ALT increased and AST increased. No subjects in the placebo group discontinued or interrupted study drug. Treatment interruption due to ALT increased and AST increased is a known effect of ELX/TEZ/IVA in the treatment of CF.

Adverse event of specific interest (AESI) were transaminase elevations and rash, in line with the known effect of ELX/TEZ/IVA and previous procedures of ELX/TEZ/IVA and TEZ/IVA. Alanine transaminase (ALT) or aspartate transaminase (AST) >3, >5, and >8 × upper limit of normal (ULN) occurred in 8 (13.6%), 3 (5.1%), and 1 (1.7%) subject(s) in the ELX/TEZ/IVA group, compared to 3 (4.9%), 1 (1.6%), and 0 subject(s) in the placebo group. No subjects had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN. These finding are comparable to the findings of the authorisation trial in children 6 though 11 years of age, study VX18-445-10.
Elevated transaminase events occurred in 6 (10.0%) subjects in the ELX/TEZ/IVA group and 3 (4.9%) subjects in the placebo group. All elevated transaminase events were mild or moderate in severity, and none were serious. Four (6.7%) subjects in the ELX/TEZ/IVA group interrupted study drug due to elevated transaminase events.

Rash events (AESI of rash) occurred in 8 (13.3%) subjects in the ELX/TEZ/IVA group and 3 (4.9%) subjects in the placebo group. The majority of rash events were mild or moderate in severity. One (1.7%) subject in the ELX/TEZ/IVA group discontinued the study drug because of a rash event. Two (3.3%) subjects in the ELX/TEZ/IVA group interrupted study drug due to rash events; both subjects resumed study drug without recurrence of rash.
Overall, the frequencies of the AESIs are in line with the frequencies found in the authorisation study VX18-445-106.

3. CHMP overall conclusion and recommendation

Study VX19-445-116 is well designed and has a sufficient duration to evaluate efficacy and safety.

Treatment with ELX/TEZ/IVA resulted in a statistically significant, and clinically relevant improvement through 24 weeks in $LCI_{2.5}$, as compared to placebo. This was supported by a clinically meaningful improvement through 24 weeks in SwCl, ppFEV1 and CFQ-R RD.

ELX/TEZ/IVA was generally safe and well tolerated for 24 weeks of treatment. No new safety concerns were identified as the data were generally consistent the safety profile in the authorisation studies of ELX/TEZ/IVA in children 6 through 11 years as well as in adults and adolescents.

The benefit-risk evaluation of Kaftrio remains positive.

☒ Fulfilled:

In view of the available data regarding safety and efficacy of treatment with ELX/TEZ/IVA in study 116 the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and **no later than 60 days** after the receipt of these conclusions.

4. Request for supplementary information

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

1. the applicant is requested to explain how the patients with values outside the in-and exclusion criteria were handled, e.g. patients with LCI2.5 < 7.5 and/or h ppFEV1< 70%.
2. The LS mean absolute change in LCI2.5 at week 24 was preferred instead of through Week 24. The applicant is requested to provide the results at D15.
3. For each of the endpoints, not all participants had data available at all timepoints. The current analysis methods assume that the data are missing at random. For each endpoint, the Applicant is requested to provide the missing data patterns over the full follow up period and provide any available details on the reasons for missing data. The Applicant is also asked to provide sufficient justification to support the assumption that the data are MAR. Further, the Applicant is requested to provide results from a sensitivity analysis for the primary endpoint based on a jump to reference missing data assumption.
4. The current study VX19-445-116 is well designed and has a sufficient duration to evaluate efficacy and safety. Because the registration study was hampered by missing data because of the Covid pandemic, it is considered that the study results are valuable to add to the SmPC. The applicant is requested to include the results. To be noted, only the results of the primary and key secondary endpoints will be accepted.

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

MAH responses to Request for supplementary information

Question 1

The applicant is requested to explain how the patients with values outside the in-and exclusion criteria were handled, e.g. patients with LCI2.5 < 7.5 and/or ppFEV1< 70%.

Applicant's response

Eligibility criteria for number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value (LCI2.5) and percent predicted forced expiratory volume in 1 second (ppFEV1) were based on Screening Visit values. Subjects with post-screening values below these thresholds (ppFEV1 <70, LCI2.5 <7.5) were still considered to have met eligibility criteria.

Overall, 14 (11.6%) subjects had ppFEV1 <70 at baseline (e.g., Day 1) and 7 (5.8%) subjects had LCI2.5 <7.5 at baseline (Table 14.1.4 and Adhoc Table 14.1.4.1).

Adhoc Table 14.1.4.1
$LCI_{2.5}$ Category at Baseline
Full Analysis Set

	Placebo N = 61	ELX/TEZ/IVA N = 60	Total N = 121
$LCI_{2.5}$ at Baseline, n (%)			
<7.5	4 (6.6)	3 (5.0)	7 (5.8)
≥7.5	57 (93.4)	57 (95.0)	114 (94.2)

- Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period.

All subjects who met the Full Analysis Set (FAS) definition (all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug) were included in the efficacy analysis, in line with the intention-to-treat (ITT) principle.

Assessment of the response

The applicant explained that the subjects with baseline values $LCI_{2.5}$ < 7.5 and/or ppFEV1< 70% were post screening and were still considered to have met eligibility criteria. Although it is acknowledged that there are usually some differences between screening and baseline values, the number of patients that were eligible but had lower values at baseline is considered rather high, i.e. 14 (11.6%) subjects with $ppFEV_1$ <70 at baseline (e.g., Day 1) and 7 (5.8%) subjects had $LCI_{2.5}$ <7.5 at baseline. Nevertheless, it is agreed that the subjects were eligible, based on most recent non-missing measurement collected before the first dose of study drug in the Treatment Period.

Conclusion: Issue resolved.

Question 2

The LS mean absolute change in $LCI_{2.5}$ at week 24 was preferred instead of through Week 24. The applicant is requested to provide the results at D15.

Applicant's response

Absolute change in $LCI_{2.5}$ at Day 15 is presented in Table 1. Results are consistent with the primary analysis of absolute change in $LCI_{2.5}$ from baseline through Week 24 (LS mean treatment difference of -2.26 [95% CI: -2.71, -1.81] for the ELX/TEZ/IVA group versus placebo).

Table 1 MMRM Analysis of Absolute Change from Baseline in $LCI_{2.5}$ at Day 15 (FAS)

	Placebo N = 61	ELX/TEZ/IVA N = 60
Baseline		
n	61	60
Mean (SD)	9.75 (1.95)	10.26 (2.22)
Absolute change at Day 15		
n	53	53
LS mean (SE)	-0.08 (0.17)	-2.23 (0.17)
95% CI of LS mean	(-0.42, 0.26)	(-2.57, -1.88)
LS mean difference (SE)	--	-2.15 (0.25)
95% CI of LS mean	--	(-2.64, -1.66)

Source: Study 116 CSR/Table 14.2.1.3

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; 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. MMRM included data from all available visits up to Week 24, with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline $LCI_{2.5}$ and weight at Screening (<30 versus ≥30 kg) 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.

Assessment of the response

The applicant provided the results of D15 as requested. The results are consistent with the results of absolute change in $LCI_{2.5}$ from baseline through Week 24.

Although the intention was to request for the results at week 24 as is mentioned in the discussion part, this information is found in Table 14.2.1.6.5 that showed that the difference in change from baseline at week 24 was -2.76 (-3.36, -2.16).

Adhoc Table 14.2.1.6.5
Sensitivity Analysis: MMRM Analysis of Absolute Change from Baseline in $LCI_{2.5}$ at Each Visit up to Week 24
with Reference-Based Imputation Multiple
Full Analysis Set

	Placebo N = 61	ELX/TEZ/IVA N = 60
Absolute change at Week 24		
n	61	60
LS mean (SE)	0.33 (0.22)	-2.43 (0.22)
95% CI of LS mean	(-0.09, 0.76)	(-2.86, -1.99)
LS mean difference (SE)	--	-2.76 (0.30)
95% CI of LS mean	--	(-3.36, -2.16)

Based on the above information, it is considered the absolute change in LCI2.5 from baseline at Week 24 is also consistent (or a slightly better) than absolute change in LCI2.5 from baseline through Week 24.

Conclusion: Issue resolved

Question 3

For each of the endpoints, not all participants had data available at all timepoints. The current analysis methods assume that the data are missing at random. For each endpoint, the Applicant is requested to provide the missing data patterns over the full follow up period and provide any available details on the reasons for missing data. The Applicant is also asked to provide sufficient justification to support the assumption that the data are MAR. Further, the Applicant is requested to provide results from a sensitivity analysis for the primary endpoint based on a jump to reference missing data assumption.

Applicant's response

Overall, analyses of missing data patterns demonstrate that the amount of missing data in Study 116 is low and support Vertex's assumption that data are missing at random. Sensitivity analyses using reference-based multiple imputation for absolute change from baseline in LCI2.5 are consistent with the primary analysis and do not affect the interpretation of results from Study 116. Additional details are provided below.

Missing data

Missing data at each visit for subjects with monotone missing data, (i.e., a visit is imputed only if all data are missing in subsequent visit[s]) and thus whose data are imputed, are presented in Adhoc Table 14.2.1.1.1 (LCI2.5), Adhoc Table 14.2.2.1.1 (SwCl), Adhoc Table 14.2.3.1.1 (CFQ-R RD score), and Adhoc Table 14.2.4.1.1 (ppFEV1).

Imputed missing data were categorized into 1 of 2 categories:

- Category 1: subjects who discontinued treatment because of either adverse events (AEs); noncompliance with study drug, death, physician decision, or because the subject refused further dosing or required prohibited medications.
- Category 2: subjects who either completed 24 weeks of treatment or discontinued treatment not due to reasons listed in Category 1.

Overall, the amount of missing data through Week 24 was low and almost all subjects with missing data were in Category 2. For LCI2.5, 16 (13.2%) subjects had monotone missing data: 1 (0.8%) subject was in Category 1 (discontinuation due to an AE) and 15 (12.4%) subjects were in Category 2. The primary reason for missing data was assessments not meeting criteria.

Because assessment of multiple-breath washout criteria was independent of the efficacy data, Vertex considers that the missing-at-random assumption is reasonable.

Similar trends were observed for sweat chloride (SwCl), Cystic Fibrosis Questionnaire - Revised (CFQ-R), and ppFEV1; the amount of missing data through Week 24 was low, and the majority of subjects with missing data were in Category 2.

Sensitivity analyses

A sensitivity analysis using reference-based multiple imputation was performed for the primary endpoint of absolute change from baseline in LCI2.5 through Week 24 (Table 2). Results were consistent with the primary analysis. A similar sensitivity analysis by visit is presented in Adhoc Table 14.2.1.6.5.

Table 2 Sensitivity Analysis: MMRM Analysis of Absolute Change From Baseline in LCI2.5 Through Week 24 With Reference-Based Multiple Imputation (FAS)

	Placebo N = 61	ELX/TEZ/IVA N = 60
Absolute change through Week 24		
n	61	60
LS mean (SE)	0.02 (0.16)	-2.30 (0.16)
95% CI of LS mean	(-0.29, 0.32)	(-2.61, -1.99)
P value within treatment	0.9139	<0.0001
LS mean difference (SE)	--	-2.32 (0.22)
95% CI of LS mean	--	(-2.76, -1.88)
P value versus Placebo	--	<0.0001

Source: Adhoc Table 14.2.1.6.4

CI: confidence interval; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LCI2.5: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement collected before the first dose of study drug in the Treatment Period. The same MMRM as the primary analysis was used, including all the data up to Week 24. Missing $LCI_{2.5}$ assessments were imputed only for visits of which all subsequent visits through Week 24 were also missing. Intermediate missing data, i.e., missing values that fell between 2 non-missing ones, were not imputed.

Assessment of the response

The applicant provided the following results.

$LCI_{2.5}$. Missing data was absent up to week 8, 1.6% (placebo) vs 5.0% (Kaftrio) at week 16, and 8.2% vs 18.4% in week 24. Virtually all this missing data was of category 2 (at most 1.7% in category 1, so at most 1.7% due to either AE, non-compliance, death, physician decision, or subject refusal or prohibited medication), and by the words of the Applicant mostly due to not meeting criteria (no further details were provided). The applicant explained that the primary reason for missing data was assessments not meeting criteria. 'Not meeting criteria' can be considered to be unrelated to the outcome because performing a valid pulmonary function test is prone to some invalid measurements due to the technical challenges.

The primary analysis for $LCI_{2.5}$ (change from baseline *through* week 24) showed an effect of -2.26 (-2.71, -1.81) and the reference based showed imputation -2.32 (-2.76, -1.88). As most missings were in the Kaftrio arm, the reference based imputation is not to expected to favour the Kaftrio arm. In table 14.2.1.6.5 also the change from baseline *at* week 24 were provided: -2.76 (-3.36, -2.16). These results thus fully support the main analysis.

Sweat Chloride: Missing data was absent up to week 8, 1.6% (placebo) vs 1.7% (Kaftrio) at week 16, 13.1% vs 5% at week 24, mostly present in category 2. Although more missingness in the placebo, this is not expected to change the large effect (-51.2 mmol/L, (-55.3, -47.1)).

CFQ-R: Missing data was absent up to week 8, 0% (placebo) vs 1.7% (Kaftrio) at week 16, 3.3% vs 3.4% at week 24, mostly present in category 2. Given the similar drop-out, the original analysis is likely robust.

ppFEV1: Missing data was absent up to week 8, 9.8% (placebo) vs 10% (Kaftrio) at week 16, 21.3% vs 20.0% at week 24, mostly present in category 2. Given the similar drop-out, the original analysis is likely robust.

Overall, robustness is considered to be shown.

Conclusion: Issue resolved

Question 4

The current study VX19-445-116 is well designed and has a sufficient duration to evaluate efficacy and safety. Because the registration study was hampered by missing data because of the Covid pandemic, it is considered that the study results are valuable to add to the SmPC. The applicant is requested to include the results. To be noted, only the results of the primary and key secondary endpoints will be accepted.

Applicant's response

Vertex acknowledges that results from Study 116 may provide additional value and agrees to include results from the primary and key secondary endpoints in the SmPC. New text to added to the product information is underlined. Current text to be deleted is ~~strikethrough~~.

Summary of product characteristics

4.8 Undesirable effects

Safety data from the following studies were consistent with the safety data observed in study 445-102.

- A 4-week, randomised, double-blind, active-controlled study in 107 patients (study 445-103).
- A 96-week, open-label safety and efficacy study (study 445-105) for patients rolled over from studies 445-102 and 445-103, with interim analysis performed on 510 patients including 271 patients with ≥48 weeks of cumulative treatment with IVA/TEZ/ELX in combination with IVA.
- An 8-week, randomised, double-blind, active-controlled study in 258 patients (study 445-104)
- A 24-week, open-label study (study 445-106) in 66 patients aged 6 to less than 12 years.
- A 24-week, randomised, placebo-controlled study (study 445-116) in 121 patients aged 6 to less than 12 years.

5.1 Pharmacodynamic properties

Pharmacodynamic effects
Effects on sweat chloride

[…]

In study 445-116 (patients aged 6 to less than 12 years who are heterozygous for the *F508del* mutation and a minimal function mutation), treatment with IVA/TEZ/ELX in combination with IVA resulted in reduction in sweat chloride through week 24, as compared to placebo. The LS mean treatment difference for the IVA/TEZ/ELX in combination with IVA group versus placebo for absolute change in sweat chloride from baseline through week 24 was -51.2 mmol/L (95% CI: -55.3, -47.1; nominal P<0.0001).

Clinical efficacy and safety

[…]

Study 445-116 was a 24-week, randomised, double-blind, placebo-controlled study in patients aged 6 to less than 12 years (mean age at baseline 9.2 years) who were heterozygous for the *F508del* mutation and a minimal function mutation. A total of 121 patients were randomised to receive either placebo or IVA/TEZ/ELX in combination with IVA. Patients who received IVA/TEZ/ELX in combination with IVA weighing <30 kg at baseline were administered two IVA 37.5 mg/TEZ 25 mg/ELX 50 mg tablets in the morning and one IVA 75 mg tablet in the evening. Patients weighing ≥30 kg at baseline were administered two IVA 75 mg/TEZ 50 mg/ELX 100 mg tablets in the morning and one IVA 150 mg tablet in the evening. At screening, patients had a $ppFEV_1$ ≥70% [mean $ppFEV_1$ at baseline of 89.3% (range: 44.6%, 121.8%)], $LCI_{2.5}$ result ≥7.5 [mean $LCI_{2.5}$ at baseline of 10.01 (range: 6.91, 18.36)], and weighed ≥15 kg.

[…]

Patients who had lung infection with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT ≥3 x ULN, or total bilirubin ≥2 x ULN), were excluded. Patients in studies 445-102 and 445-103 were eligible to roll over into a 96-week open label extension study (Study 445 105). Patients in studies 445 104, ~~and~~ 445 106, and 445-116 were eligible to roll over into separate open-label extension studies.

Paediatric population

Paediatric patients aged 6 to <12 years

[…]

Study 445-116

In study 445-116, treatment with IVA/TEZ/ELX in combination with IVA resulted in statistically significant improvement through 24 weeks in the primary endpoint ($LCI_{2.5}$). The LS mean treatment difference for the IVA/TEZ/ELX in combination with IVA group versus placebo for the absolute change in $LCI_{2.5}$ from baseline through week 24 was -2.26 (95% CI: -2.71, -1.81; P<0.0001).

[…]

Assessment of the response
The applicant agreed to include the main results of study 116 in the SmPC. The proposed text in section 4.8 and 5.1 is acceptable.

Conclusion: Issue resolved

For the update of the SmPC with the results of study VX19-445-116 as agreed upon during this P46 procedure, the applicant should submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 (see section 3).