22 February 2024
EMA/CHMP/528665/2023
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/P46/016

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
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List of abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BfArM	German Federal Institute for Drugs and Medical Devices
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CI	confidence interval
CK	creatine kinase
COVID-19	coronavirus disease
DBP	diastolic blood pressure
ECG	electrocardiogram
ELX	elexacaftor
F/MF	heterozygous for F508del mutation and a minimal function mutation
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
IPD	important protocol deviation
IRB	institutional review board
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
LFT	liver function test
LS	least squares
max	maximum
min	minimum
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size
N1	number of subjects with at least 1 non-missing measurement during the treatment-emergent period
OLE	open-label extension
OL FAS	open-label full analysis set
PD	pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbation
PK	pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PY	patient-years
q12h	once every 12 hours
qd	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	System Organ Class
SwCl	sweat chloride
TEAEs	treatment-emergent adverse events
TEZ	tezacaftor
ULN	upper limit of normal
USA	United States of America

1. Introduction

On 19-9-2023, the MAH submitted a completed paediatric study, Study VX20-445-119, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

A line listing is not provided with this application as Study VX20-445-119 is not part of a development program for Kaftrio and is submitted standalone.

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. The indication was extended to children with CF aged 6 years through 11.

Recently, the Committee for Medicinal Products for Human Use (CHMP) recommended the approval of two new presentations of Kaftrio (60mg/40mg/80mg and 75mg/50mg/100mg granules in sachet) for use in children aged 2 to 5 years of age.

The indication for Kaftrio granules will be as follows:

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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.

Within this procedure, the Applicant submitted the results of study VX20-445-119.

The MAH stated that Study VX20-445-119 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study VX19-445-119, 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 fixed-dose combination (FDC) tablet
- 150 mg IVA tablet
- 75 mg IVA tablet

All these tablets are authorised for this population and age group. The applied posology aligns with the dose approved for patients aged ≥ 6 years.

Table 1 Dosing recommendation for patients aged 6 years and older

Age/Weight	Morning dose	Evening dose
6 to <12 years, <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,≥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

Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
≥6 to <12 years			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h

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

3. Clinical aspects

CHMP comment

The MAH has stated that the structure of the Abbreviated Clinical Study Report was prepared in compliance with the FDA Guidance Document "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications." Selected sections are therefore omitted or include only a cross-reference to applicable summary tables, figures, and listings submitted with this abbreviated clinical study report (aCSR). Standard section numbering was maintained.

As this is a submission for the EU, the CSR is to be in compliance with the EMA Guidelines. Where necessary, additional information will be requested to comply with EMA standards.

3.1.1. Introduction

The MAH submitted a final report(s) for:

Study VX20-445-119: A Phase 3b Open-label Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects Ages 6 Years and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

3.1.2. Clinical study

Clinical study number and title

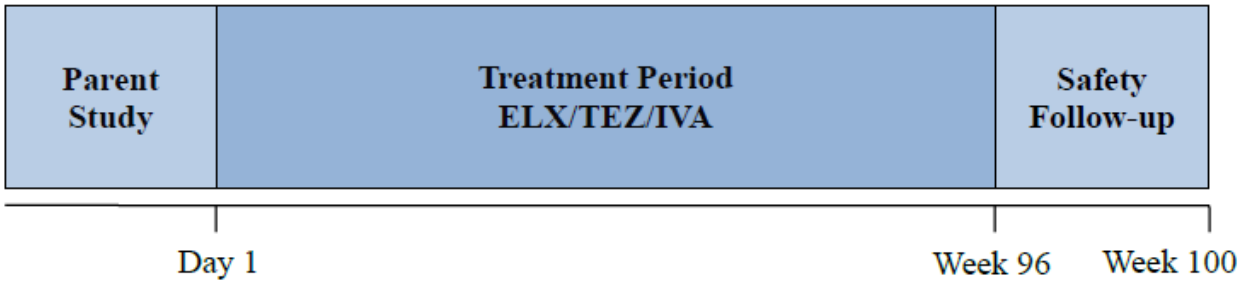
EudraCT Number: 2020-001404-42

Study VX20-445-119: A Phase 3b Open-label Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects Ages 6 Years and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

Description

This was a Phase 3b, multicenter, open-label study for subjects who completed the parent study (VX19-445-116 [Study 116]) and met eligibility criteria for this study. A schematic of the study design is shown in Figure 1.

Figure 1 VX20-445-119 Study Design



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: Figure not drawn to scale.

CHMP comments

Parent study 116 has been submitted previously (EMEA/H/C/005269/P46/008).

Methods

Study participants

Male and female CF subjects 6 years of age or older with F/MF genotypes who (1) completed study drug treatment in the parent study or (2) did not permanently discontinue study drug, but completed all treatment period study visits in the parent study (Study 116) and met eligibility criteria for this study.

Table 2 Key Eligibility Criteria in Study 119

Inclusion Criteria	Exclusion Criteria

• Did not withdraw consent from Study 116
• Met at least 1 of the following criteria:
  ○ Completed study drug treatment in the parent study.
  ○ Had study drug interruption(s) in the parent study, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of the parent study.
• Willing to remain on a stable CF treatment regimen through completion of study participation.
	• History of any comorbidity that could confound the results of the study or pose an additional risk in administering study drug to the subject
	• History of drug intolerance in Study 116 that would pose an additional risk in administering study drug to the subject
	• Pregnant or breast-feeding females
	• Current participation in an investigational drug trial (other than Study 116)

Sources: Study 119 Protocol/Sections 8.1 and 8.2
CF: cystic fibrosis

CHMP comments

The main inclusion criteria of the parent Study 116 were ppFEV1 ≥ 70% or $LCI_{2.5}$ ≥7.5. The inclusion of patients with $LCI_{2.5}$ ≥ 7.5 indicates that the small airways had to be impaired.

Treatments

Subjects received ELX/TEZ/IVA at the weight-appropriate dosage levels shown in Table 3based on their weight at Day 1.

Table 3 Treatment Period Dosages

Subject Age Weight	ELX Dosage	TEZ Dosage	IVA Dosage
≥6 to <12 years			
<30 kg	100 mg qd	50 mg qd	75 mg q12h
≥30 kg	200 mg qd	100 mg qd	150 mg q12h
≥12 years			
All weights	200 mg qd	100 mg qd	150 mg q12h

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

If a subject entered the current study weighing <30 kg and subsequently weighed ≥30 kg at 2 consecutive clinic visits (excluding unscheduled visits), the dose was adjusted to the higher dose of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h for the remainder of the study, starting with the second visit where subject's weight was ≥30 kg.

Subjects ≥12 years of age received a dose of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h, starting from the first study visit at which the subject was ≥12 years old.

Subjects should remain on a stable treatment regimen for their CF through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before Day 1. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:

- Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule.
- Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study.

Table 4 Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers of CYP3A and moderate and strong inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, are prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drugs in the parent study and this study	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

CYP: cytochrome P450; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

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

CHMP comments

The rules for concomitant stable CF medication, restriction of CYP3A inducers and CYP3A inhibitors were all acceptable. Co-administration of ELX/TEZ/IVA with moderate and strong CYP3A inducers and inhibitors was restricted in this study, although dosing modification of CYP3A inhibitors are currently described in the approved SmPC. Nevertheless, the same restrictions were applied in the pivotal studies and these more strict rules are considered acceptable for the purpose of a study.

Objective(s)

Primary Objective

To evaluate the long-term safety and tolerability of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with cystic fibrosis (CF).

Secondary Objectives

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

Outcomes/endpoints

Primary Endpoint

Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Secondary Endpoints

- Absolute change in sweat chloride (SwCl) from baseline
- Absolute change in lung clearance index2.5 (LCI2.5) from baseline

Other Endpoints

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

The baseline value, unless otherwise specified, for the long-term safety analysis will be the TC safety baseline, defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ELX/TEZ/IVA *either in the parent study or the open label study*, as applicable.

The baseline value for the long-term efficacy analysis, unless otherwise specified, will be the parent study baseline, defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the parent study. For assessments collected in duplicate or triplicate, the baseline will be defined as the average of nonmissing values.

CHMP comments

The primary safety endpoints are standard safety endpoints. The secondary efficacy endpoints are agreed, as they measure relevant aspects and goals for a treatment in CF. LCI2.5 is a sensitive measurement for impairment in smaller airways, the part that is affected in the beginning of CF. Defining the baseline (e.g., for duration) for safety using the ELX/TEZ/IVA exposure is understood. Using the parent study baseline as baseline value for the long-term efficacy analysis is acknowledged, because it will facilitate comparison of efficacy in patients starting directly on ELX/TEZ/IVA versus those with delayed start.

Sample size and power

The primary objective of the study is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. This is an OLE study that will enrol subjects who did not discontinue study drug during the Treatment Period in parent study (445-116) and meet eligibility criteria. Approximately 108 subjects are expected to enrol in this OLE.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

ANALYSIS SETS

The following analysis sets are defined: Open-label (OL) All Subjects Set, 116 and OL Full Analysis Set, and OL Safety Set.

OL All Subjects Set

The OL All Subjects Set (OL-AS) will include all subjects who were enrolled (defined as subject having data in the clinical database) in this OLE study. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

116 and OL Full Analysis Set

The Study 116 Full Analysis Set (116-FAS) is defined the same as the FAS definition in the SAP of Study 116.

The OL Full Analysis Set (OL-FAS) will include all enrolled subjects who have received at least 1 dose of study drug in this OLE study. The OL-FAS will be used to summarize subject demographics and baseline characteristics and for all efficacy analyses unless otherwise specified.

OL Safety Set

The OL Safety Set (OL-SS) will include all subjects who have received at least 1 dose of study drug in this OLE study. The OL-SS will be used for all safety analyses unless otherwise specified.

ANALYSIS METHOD

Absolute change in SwCl from baseline:

The mixed-effects model for repeated measures (MMRM) for the parent study 116-FAS will be same as that described in the SAP for Study 116. In the MMRM for the OL-FAS, the absolute change from baseline in SwCl will be the dependent variable. The model will include treatment group (as randomized in the parent study), visit, and treatment-by-visit interaction as fixed effects, with continuous baseline $LCI_{2.5}$ from the parent study and weight at Screening (<30 versus ≥30 kg) of the parent study as covariates.

The repeated-measures analysis will be based on the restricted maximum likelihood method assuming an unstructured covariance structure to model the within-subject errors. The denominator degrees of freedom will be based on the method proposed by Kenward-Roger. If the model fails to converge due to the unstructured covariance assumption, a compound symmetry covariance structure will be used to model the within-subject errors. In the MMRM approach, assuming that the data are missing at random, no imputation of missing data will be performed.

Absolute change in $LCI_{2.5}$ from baseline:

Analysis of this endpoint will be based on an MMRM similar to the analysis of the absolute change from baseline in SwCl. A descriptive summary of raw values and absolute changes from baseline will also be presented.

Percent predicted forced expiratory volume in 1 second (ppFEV1):

The predicted FEV1 will be calculated using the Global Lung Function Initative (GLI).

Analysis of this endpoint will be based on an MMRM similar to the analysis of the absolute change in SwCl.

The primary analysis will use the spirometry data obtained at clinic only. An additional analysis may be performed to include all available spirometry data obtained at clinic and obtained at home, if the spirometry data obtained at home are assessed to be reasonably consistent with the spirometry data obtained at clinic.

Cystic Fibrosis Questionnaire-Revised (CFQ-R):

The CFQ-R is a validated CF-specific instrument that measures quality-of-life domains. This study utilizes four different versions of CFQ-R:

- CFQ-R for Children ages 6 to 11
- CFQ-R for Children ages 12 and 13

• CFQ-R for Adolescents and Adults (subjects 14 years and older)

• CFQ-R for Parents/Caregivers (subjects 13 years and younger)

Analysis of this endpoint will be based on an MMRM similar to the analysis of the absolute change in SwCl.

Sensitivity and supportive analysis of secondary endpoints

No sensitivity or supportive analysis is planned for the secondary endpoints.

Subgroup Analysis

No subgroup analysis is planned for the secondary endpoints.

CHMP comments

In study 116, patients were randomised to placebo or ELX/TEZ/IVA. Immediately after completion study 116, all patients in this OLE (study 119) received ELX/TEZ/IVA. Therefore, a 'catch-up' effect is expected in those originally randomised to placebo arm in study 116. Therefore, the 3rd effect estimate of the treatment group and its interactions with visit are of interest to see the speed and extent to which 'delayed start' of treatment influences the end result. The specification of the MMRM are suitable to estimate this and estimates can be compared to those in study 116 due to the same specification as in study 116.

In parent study 116, $LC_{2.5}$ at baseline (and weight) were used as covariates in the CFQ, ppFEV1, sweat chloride (and $LC_{2.5}$) analyses. This was also the case in this OLE study.

Results

Participant flow

Subject disposition is summarized in Table 5.

Table 5 Subject Disposition (OL All Subjects Set)

Disposition/Reason	Placebo in Study 116 n (%)	ELX/TEZ/IVA in Study 116 n (%)	Any ELX/TEZ/IVA n (%)
OL All Subjects Set	61	59	120
OL FAS	61	59	120
OL Safety Set	61	59	120
Completed treatment	56 (91.8)	54 (91.5)	110 (91.7)
Prematurely discontinued treatment	5 (8.2)	5 (8.5)	10 (8.3)
Reason for discontinuation of treatment			
AE	1 (1.6)	0	1 (0.8)
Subject refused further dosing (not due to AE)	1 (1.6)	0	1 (0.8)
Commercial drug is available for subject	2 (3.3)	5 (8.5)	7 (5.8)
Other non-compliance	1 (1.6)	0	1 (0.8)
Completed study	56 (91.8)	54 (91.5)	110 (91.7)
Prematurely discontinued study	5 (8.2)	5 (8.5)	10 (8.3)
Reason for discontinuation from study			
AE	1 (1.6)	0	1 (0.8)
Withdrawal of consent (not due to AE)	2 (3.3)	0	2 (1.7)
Commercial drug is available for subject	2 (3.3)	5 (8.5)	7 (5.8)

Source: Table 14.1.1

AE: adverse event; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; OL: open-label; OLE: open-label extension; TEZ: tezacaftor

Notes: OL All Subjects Set is defined as all subjects who were enrolled (defined as subjects having data in the clinical database) in this OLE study. OL Safety Set is defined as all subjects who received at least 1 dose of study drug in this OLE study. OL Full Analysis Set is defined as all enrolled subjects who received at least 1 dose of study drug in this OLE study. Percentages are based on the number of subjects in the OL Safety Set. Treatment assignment for subjects is based on the actual treatment received in the parent study.

CHMP comments

A total of 10 (8.3%) subjects prematurely discontinued study treatment; for most of the subjects the reason was that commercial drug became available (n=7 (5.8%). Only 1 subject (0.8%) withdrew because of an AE. This is additional to the 1 subject that already withdrew due to AE on ELX/TEZ/IVA in study 116 (i.e. within 24 weeks). Therefore, it can be concluded that ELX/TEZ/IVA was well accepted.

Recruitment

Subjects were enrolled at 34 sites in Australia, Canada, Denmark, France, Germany, Israel, Netherlands, Spain, Switzerland, and the United Kingdom.

Conduct of Study

Changes in Conduct of Study

Country-specific amendments were prepared for 2 countries (see Table 6 for details).

Table 6 Summary of Study 119 Protocol Changes

Protocol Version	Date	Key Changes
1.0	26 June 2020	Original Version
1.1DE	01 September 2020	Original Version in Germany
1.2FR	01 September 2020	Original Version in France
1.3DE	03 February 2021	Based on feedback from BfArM: • Updated certain exclusion criteria related to safety: ○ Provided examples of comorbidities that might pose an additional risk in administering study drug to the subject ○ For exclusion related to medical history that might pose an additional risk to the subject, removed conditional "in the opinion of the investigator" ○ Added an exclusion criterion for use of restricted medications, unless a subject is on a study drug interruption at the time of rollover ○ Added an exclusion criterion for the scenario in which the subject or a close relative of the subject is directly involved with the conduct of the study at that site • Removed option for remote informed consent. • Removed text stating that it is the responsibility of the investigator or designee to promptly notify the local IRB/IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

BfArM: German Federal Institute for Drugs and Medical Devices; ELX: elexacaftor; IEC: independent ethics committee; IRB: institutional review board; IVA: ivacaftor; TEZ: tezacaftor

CHMP comments

In addition to the above table, twice a new version was written. The date of Protocol Version 3.0 is 29 July 2020.

Furthermore, at the request of the German health authority (BfArM), protocol version 1.3 DE included additional exclusion criteria to more closely align with those in the parent study protocol (Study VX19-445-116 [Study 116]). Although the changes could had have led to disparity between the included subject, the applicant confirmed that the changed exclusion criteria did not prevent any subjects to roll over.

Changes in Planned Analyses

There were no changes to analyses described in the statistical analysis plan (SAP) Version 1.0.

Changes in Study Conduct Due to COVID-19

Vertex implemented safety measures to provide subjects the opportunity to continue participation in this study while ensuring their safety by minimizing the risk of coronavirus disease (COVID-19) exposure through travel. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to study integrity.

Implemented measures included shipment of study drug from site to subject's home, telephone/video call for safety assessments, in home assessments, use of local laboratories for safety assessments, at home urine pregnancy testing, verbal re-consenting, remote re-consenting, remote monitoring/source data verification, and addition of electronic data capture visit type forms. These measures were

enabled based on country and local regulations and site-level considerations (e.g., site closure due to COVID-19).

In addition to their usual review of central laboratory data, investigators were responsible for reviewing local laboratory data to identify potential AEs.

In general, there was minimal impact by COVID-19 on study conduct.

Protocol Deviations

An important protocol deviation (IPD) was 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.

In total, there were 4 (3.3%) subjects with IPDs:

- 3 subjects had IPDs related to informed consent
- 1 subject had IPDs related to investigational product: this subject received incorrect dose of study drug between week 72 and week 84. Dose received during this period was ELX/TEZ/IVA 100/50/75 mg. But the planned dose should be 200/100/150 mg. According to Primary SC, dose not increased between week 72 to week 84 due to pharmacy process (the weight from the previous visit was used for the visit immediately followed the previous visit). Subject was greater than 30 kg at week 60 and week 72 but did not move to adult dose until week 84 visit.

CHMP comments

The IPD related to investigational product concerned the underdosing during a short period (12 weeks). The reported IPDs are not considered to impact the overall study results importantly.

Baseline data

Demographics are summarized in Table 7 and baseline characteristics are summarized in Table 8.

Most participants were female (57.5%), white (72.5%); the mean age of participants was 9.1 years.

Table 7 Subject Demographics at Parent Study Baseline (OL FAS)

Demographic	Placebo in Study 116 N = 61	ELX/TEZ/IVA in Study 116 N = 59	Any ELX/TEZ/IVA N = 120
Sex, n (%)			
Male	26 (42.6)	25 (42.4)	51 (42.5)
Female	35 (57.4)	34 (57.6)	69 (57.5)
Childbearing potential at parent study baseline, n (%)			
Yes	17 (48.6)	19 (55.9)	36 (52.2)
No	18 (51.4)	15 (44.1)	33 (47.8)
Age at parent study baseline (years)			
n	61	59	120
Mean (SD)	9.2 (1.7)	9.0 (1.8)	9.1 (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 (76.3)	87 (72.5)
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)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (1.6)	0	1 (0.8)
Not collected per local regulations	18 (29.5)	10 (16.9)	28 (23.3)
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 (81.4)	90 (75.0)
Not collected per local regulations	19 (31.1)	10 (16.9)	29 (24.2)
Country, n (%)			
Australia	5 (8.2)	6 (10.2)	11 (9.2)
Canada	6 (9.8)	7 (11.9)	13 (10.8)
Denmark	3 (4.9)	0	3 (2.5)
France	8 (13.1)	5 (8.5)	13 (10.8)
Germany	16 (26.2)	15 (25.4)	31 (25.8)
Israel	1 (1.6)	4 (6.8)	5 (4.2)
Netherlands	6 (9.8)	1 (1.7)	7 (5.8)
Spain	2 (3.3)	6 (10.2)	8 (6.7)
Switzerland	7 (11.5)	5 (8.5)	12 (10.0)
United Kingdom	7 (11.5)	10 (16.9)	17 (14.2)

Source: Table 14.1.3

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

Notes: Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period of the parent study. Percentages of childbearing women are based on the number of women in the OL FAS.

Table 8 Parent Study Baseline Characteristics (OL FAS)

Characteristic	Placebo in Study 116 N = 61	ELX/TEZ/IVA in Study 116 N = 59	Any ELX/TEZ/IVA N = 120
Weight (kg)			
n	61	59	120
Mean (SD)	29.8 (8.6)	28.9 (7.6)	29.3 (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	59	120
Mean (SD)	-0.29 (0.96)	-0.27 (1.00)	-0.28 (0.97)
Median	-0.32	-0.27	-0.29
Min, max	-3.42, 1.95	-2.46, 1.52	-3.42, 1.95
Height (cm)			
n	61	59	120
Mean (SD)	134.6 (13.3)	132.1 (11.7)	133.4 (12.5)
Median	133.5	131.0	132.5
Min, max	99.7, 163.3	109.4, 159.4	99.7, 163.3
Height-for-age z-score			
n	61	59	120
Mean (SD)	0.01 (1.26)	-0.16 (1.02)	-0.07 (1.15)
Median	0.14	-0.16	0.02
Min, max	-6.36, 2.19	-2.55, 1.90	-6.36, 2.19
BMI (kg/m^2)			
n	61	59	120
Mean (SD)	16.11 (2.32)	16.28 (1.83)	16.19 (2.09)
Median	15.65	15.86	15.82
Min, max	13.04, 27.86	13.54, 21.91	13.04, 27.86
BMI-for-age z-score			
n	61	59	120
Mean (SD)	-0.39 (0.92)	-0.17 (0.85)	-0.28 (0.89)
Median	-0.33	-0.19	-0.26
Min, max	-2.57, 2.14	-1.88, 1.59	-2.57, 2.14
$LCI_{2.5}$ at Screening Visit in parent study, n (%)			
<10	35 (57.4)	34 (57.6)	69 (57.5)
≥10	26 (42.6)	25 (42.4)	51 (42.5)
Weight (kg) at Screening Visit in parent study, n (%)			
<30	38 (62.3)	39 (66.1)	77 (64.2)
≥30	23 (37.7)	20 (33.9)	43 (35.8)
Sweat chloride (mmol/L) at parent study baseline			
n	61	59	120
Mean (SD)	102.6 (8.6)	102.8 (10.0)	102.7 (9.3)
Median	104.0	103.5	103.8
Min, max	83.5, 123.0	77.0, 123.5	77.0, 123.5

$LCI_{2.5}$ at parent study baseline			
n	61	59	120
Mean (SD)	9.75 (1.95)	10.21 (2.20)	9.98 (2.08)
Median	9.14	9.67	9.40
Min, max	6.91, 15.75	7.13, 18.36	6.91, 18.36
$ppFEV_1$ category at parent study baseline, n (%)			
<70	10 (16.4)	4 (6.8)	14 (11.7)
≥70 to ≤90	23 (37.7)	19 (32.2)	42 (35.0)
>90	28 (45.9)	36 (61.0)	64 (53.3)
$ppFEV_1$ at parent study baseline			
n	61	59	120
Mean (SD)	87.2 (15.8)	91.6 (13.8)	89.4 (15.0)
Median	89.6	93.0	91.9
Min, max	55.8, 119.6	44.6, 121.8	44.6, 121.8
CFQ-R respiratory domain score (Child's version) at parent study baseline			
n	61	59	120
Mean (SD)	82.7 (14.1)	86.0 (11.5)	84.3 (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 (71.2)	83 (69.2)
No	20 (32.8)	17 (28.8)	37 (30.8)
Prior use of azithromycin[a], n (%)			
Yes	9 (14.8)	10 (16.9)	19 (15.8)
No	52 (85.2)	49 (83.1)	101 (84.2)
Prior use of inhaled antibiotic[a], n (%)			
Yes	8 (13.1)	15 (25.4)	23 (19.2)
No	53 (86.9)	44 (74.6)	97 (80.8)
Prior use of any bronchodilator[a], n (%)			
Yes	46 (75.4)	37 (62.7)	83 (69.2)
No	15 (24.6)	22 (37.3)	37 (30.8)
Prior use of any inhaled bronchodilator[a], n (%)			
Yes	46 (75.4)	37 (62.7)	83 (69.2)
No	15 (24.6)	22 (37.3)	37 (30.8)
Prior use of any inhaled hypertonic saline[a], n (%)			
Yes	46 (75.4)	45 (76.3)	91 (75.8)
No	15 (24.6)	14 (23.7)	29 (24.2)
Prior use of any inhaled corticosteroids[a], n (%)			
Yes	18 (29.5)	15 (25.4)	33 (27.5)
No	43 (70.5)	44 (74.6)	87 (72.5)

Source: Table 14.1.4

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

Notes: Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period of the parent study.

[a] Includes medications administered during 56 days prior to the first dose of study drug in the Treatment Period of the parent study.

Number analysed

The final number of subjects in each analysis set is provided in Table 9.

Table 9 Analysis Populations

	Placebo in Study 116 n	ELX/TEZ/IVA in Study 116 n	Any ELX/TEZ/IVA n
OL All Subjects Set	61	59	120
OL Full Analysis Set	61	59	120
OL Safety Set	61	59	120

Source: Table 14.1.1
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; OL: open-label; OLE: open-label extension; TEZ: tezacaftor
Notes: OL All Subjects Set: all subjects who were enrolled (defined as subjects having data in the clinical database) in this OLE study; OL Safety Set: all subjects who received at least 1 dose of study drug in this OLE study; OL Full Analysis Set: all enrolled subjects who received at least 1 dose of study drug in this OLE study. Treatment assignment for subjects is based on the actual treatment received in the parent study.

Efficacy results

Primary Efficacy Endpoint

Not applicable since efficacy was not a primary objective.

Secondary Efficacy Endpoints

Absolute Change in SwCl from Baseline

Change from parent study baseline in SwCl is presented in Table 10 and Figure 2.

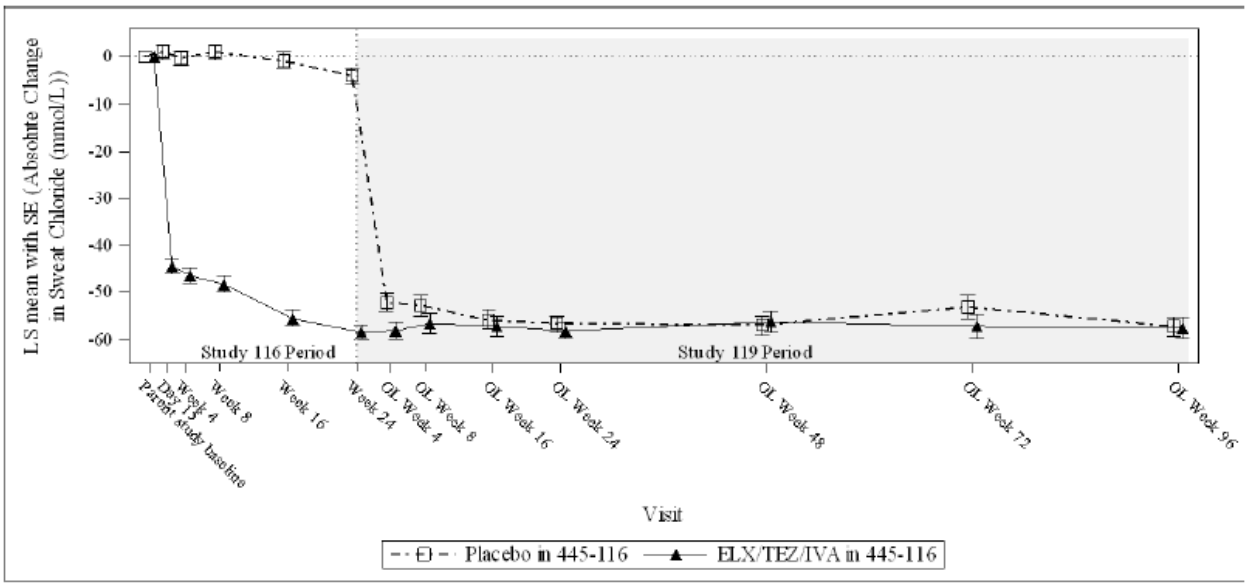
At Week 96, LS mean change in SwCl from parent study baseline was -57.3 (95% CI: -61.6, -52.9) and -57.5 (95% CI: -62.0, -53.0) mmol/L for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively.

Table 10 MMRM Analysis of Absolute Change from Parent Study Baseline in SwCl up to OL Week 96 (Study 116 FAS and OL FAS)

Visit	Placebo in Study 116	ELX/TEZ/IVA in Study 116
Parent study baseline		
n	61	60
Mean (SD)	102.6 (8.6)	102.8 (10.0)
Absolute change at OL Week 96		
n	52	46
LS mean (SE)	-57.3 (2.2)	-57.5 (2.3)
95% CI of LS mean	(-61.6, -52.9)	(-62.0, -53.0)

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; OL: open-label; SwCl: sweat chloride; TEZ: tezacaftor
Notes: Parent study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study. For the parent study, the MMRM was the same as the parent study analysis. For the OLE study, the MMRM includes data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, parent study baseline $LCI_{2.5}$, and weight at screening (<30 versus ≥30 kg) of the parent study 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 Sweat Chloride (mmol/L) at Each Visit (Study 116 FAS and OL FAS)



Source: Figure 14.2.1

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; n: size of subsample; N: total sample size; OL: open-label; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study. For the parent study, the MMRM was the same as the parent study analysis. For the OLE study, the MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, parent study baseline $LCI_{2.5}$, and weight at screening (<30 versus ≥30 kg) of the parent study 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.

CHMP comments

The results are presented as changes from baseline of parent study. LS mean change in SwCl from parent study baseline was comparable for the two groups at the end of Study 119, i.e. -57.3 and -57.5 in placebo in study 116 group and ELX/TEZ/IVA group, respectively. The change is of the same magnitude as the observed effect in the pivotal authorisation study in adults and adolescents, Study 102, (-41.8 mmol/l) and the authorisation study in children 6 through 11 years, Study 106, (-60.9 mmol/L) and Study 116 (-51.2). The observed changes from baseline are clinically relevant and the decrease obtained in study 116 was maintained during study 119.

Absolute Change in LCI2.5 from Baseline

Change from parent study baseline in LCI2.5 is presented in Table 11 and Figure 3.

At Week 96, LS mean change in LCI2.5 from parent study baseline was -1.74 (95% CI: -2.09, -1.38) and -2.35 (95% CI: -2.72, -1.97) for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively.

Table 11 MMRM Analysis of Absolute Change from Parent Study Baseline in LCI2.5 up to OL Week 96 (Study 116 FAS and OL FAS)

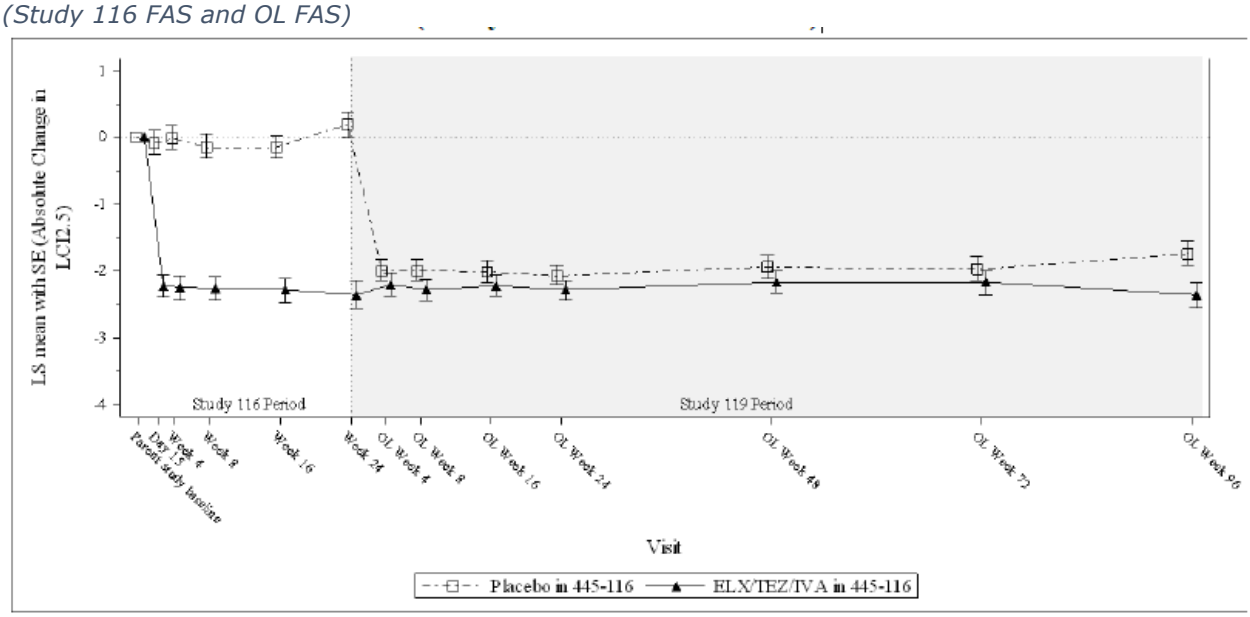
Analysis	Placebo in Study 116	ELX/TEZ/IVA in Study 116
Parent study baseline		
n	61	60
Mean (SD)	9.75 (1.95)	10.26 (2.22)
Absolute change at OL Week 96		
n	56	48
LS mean (SE)	-1.74 (0.18)	-2.35 (0.19)
95% CI of LS mean	(-2.09, -1.38)	(-2.72, -1.97)

Source: Table 14.2.2.2

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; n: size of subsample; MMRM: mixed-effects model for repeated measures; N: total sample size; OL: open-label; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study. For the parent study, the MMRM was the same as the parent study analysis. For the OLE study, the MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, parent study baseline $LCI_{2.5}$, and weight at screening (<30 versus ≥30 kg) of the parent study 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 LCI2.5 at Each Visit – (Study 116 FAS and OL FAS)



Source: Figure 14.2.2

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; OL: open-label; OLE: open-label extension; TEZ: tezacaftor

Notes: Parent study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study. For the parent study, the MMRM was the same as the parent study analysis. For the OLE study, the MMRM included data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment-by-visit as fixed effects, parent study baseline $LCI_{2.5}$ and weight at screening (<30 versus ≥30 kg) of the parent study 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.

CHMP comments

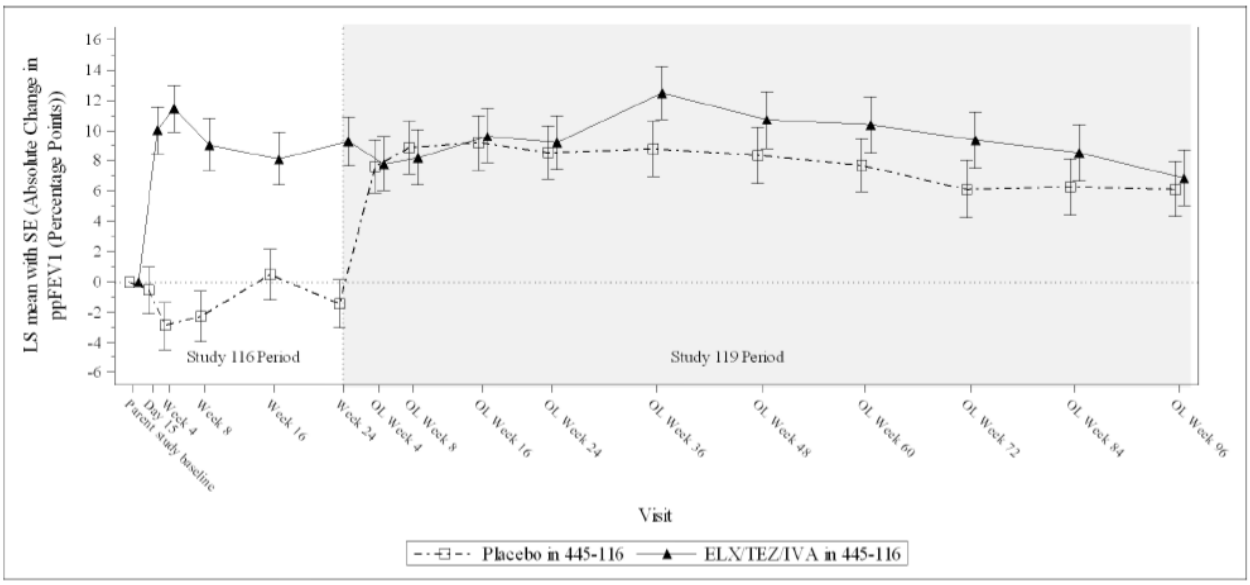
The results are presented as changes from baseline of parent study. LS mean change in $LCI_{2.5}$ from parent study baseline was generally comparable for the two groups at the end of Study 119, i.e. -1.74 and -2.35 in placebo in study 116 group and ELX/TEZ/IVA group, respectively. A change from baseline > -1 is considered clinically relevant. Missing data at week 96 was 9-20%. The change is also similar as observed in the authorisation study in children 6 through 11 years (-1.71) and Study 116 (-2.26). $LCI_{2.5}$ was not measured in Study 102. The decrease obtained in study 116 was maintained during study 119.

Other Endpoints

Absolute Change in ppFEV1 from Baseline

Change from parent study baseline in ppFEV1 is presented in Figure 4. At Week 96, LS mean change in ppFEV1 from parent study baseline was 6.1 (95% CI: 2.6, 9.7) and 6.9 (95% CI: 3.2, 10.5) percentage points for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively.

Figure 4 MMRM Analysis of Absolute Change from Parent Study Baseline in ppFEV1 (Percentage Points) at Each Visit - Parent Study and OLE Study Study 116 Full Analysis Set and OL Full Analysis Set



- Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study.
- For the parent study, the MMRM is the same as the parent study analysis. For the OLE study, the MMRM includes data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment*visit as fixed effects, parent study baseline $LCI_{2.5}$ and weight at screening (<30 versus ≥30 kg) of the parent study as covariates. Covariance structure=CS, DF=Kenward-Roger.

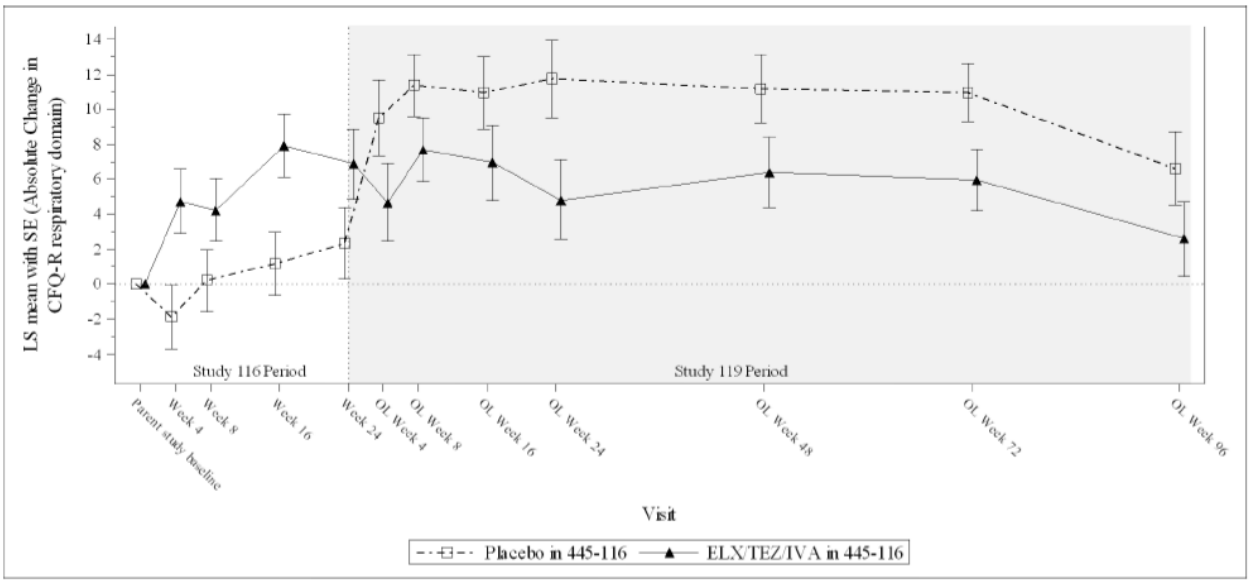
CHMP comments

The results are presented as changes from baseline of parent study. LS mean change in FEV1 from parent study baseline was generally comparable for the two groups at the end of Study 119, i.e. 6.1% and 6.9% in placebo in study 116 group and ELX/TEZ/IVA group, respectively. Of note, 32-37% had missing data at week 96. The change is slightly less than observed in the pivotal authorisation study in adults and adolescents (13.9) and the authorisation study in children 6 through 11 years (10.2%), and also somewhat lower than in Study 116 (9.5%), but the changes are still clinically relevant, especially from the perspective that the current study has a duration of 96 weeks.

Absolute Change in CFQ-R RD from Baseline

Change from parent study baseline in CFQ-R RD score is presented in Figure 5. LS mean change from parent study baseline ranged from 6.6 to 11.7 in the placebo arm of the parent study and 2.6 to 7.7 in the ELX/TEZ/IVA arm of the parent study. At Week 96, LS mean change in CFQ-R RD score from parent study baseline was 6.6 (95% CI: 2.5, 10.8) and 2.6 (95% CI: -1.6, 6.8) points for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively.

Figure 5 MMRM Analysis of Absolute Change from Parent Study Baseline in CFQ-R Respiratory Domain Score at Each Visit - Parent Study and OLE Study Study 116 Full Analysis Set and OL Full Analysis Set



- Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study.
- For the parent study, the MMRM is the same as the parent study analysis. For the OLE study, the MMRM includes data up to OL Week 96, with treatment group (as randomized in parent study), visit, and treatment*visit as fixed effects, parent study baseline $LCI_{2.5}$ and weight at screening (<30 versus ≥30 kg) of the parent study as covariates. Covariance structure=UN, DF=Kenward-Roger.

CHMP comments

The results are presented as changes from baseline of parent study. LS mean change in CFQ-R RD from parent study baseline was better in the placebo in study 116 group than in ELX/TEZ/IVA group at Week 96 of Study 119, i.e., 6.6 and 2.6 points in placebo in study 116 group and ELX/TEZ/IVA group, respectively. Missing data at week 96 was limited (7-10%). The change from baseline is similar to the change observed in children from 6 to 11 years (7.0) but lower than in the change from baseline observed in adults and adolescents after 24 weeks (17.5 points), in the authorisation study (study 116) . For the ELX/TEZ/IVA arm in study 116, the results were somewhat lower through the study 116 and study 119, but after the total exposure time there was still a benefit. Although the benefit seems low after 120 weeks, the change in CFQ-R would be still an advantage over the natural history of CF. Overall, the effect is clinically relevant.

Safety results

Extent of Exposure

The OL Safety Set included 120 subjects who had a mean exposure of 92.9 weeks, representing 232.2 patient-years of exposure (Table 12).

Table 12 Summary of Exposure (OL Safety Set)

Category	Any ELX/TEZ/IVA N = 120
Total exposure (patient weeks)	11146.1
Total exposure (patient years)	232.2
Exposure duration (weeks)	
n	120
Mean (SD)	92.9 (12.4)
Median	96.0
Min, max	8.1, 99.1
Exposure duration by interval, n (%)	
≤24 weeks	1 (0.8)
>24 to ≤48 weeks	1 (0.8)
>48 to ≤72 weeks	5 (4.2)
>72 to ≤96 weeks	61 (50.8)
>96 weeks	52 (43.3)

Source: Table 14.1.7

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; OLE: open-label extension; TEZ: tezacaftor

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

Summary of Adverse Events

One hundred and eighteen (98.3%) subjects had at least 1 AE. Most AEs were mild or moderate in severity. Eight (6.7%) subjects had at least 1 severe AE. There were no life-threatening AEs or deaths. Thirteen (10.8%) subjects had serious adverse events (SAEs), 1 (0.8%) of whom had an SAE that was considered to be related to study drug. Ten (8.3%) subjects interrupted ELX/TEZ/IVA due to AEs, and 1 (0.8%) subject discontinued ELX/TEZ/IVA due to AEs. (Table 13)

Table 13 Overview of AEs (OL Safety Set)

Category	Any ELX/TEZ/IVA N = 120 n (%)	Events/100PY
Number of AEs (total)	1648	--
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with any AEs	118 (98.3)	707.80
Subjects with AEs by strongest relationship		
Not related	30 (25.0)	--
Unlikely related	32 (26.7)	--
Possibly related	55 (45.8)	--
Related	1 (0.8)	--
Subjects with AEs by maximum severity		
Grade 1/Mild	52 (43.3)	--
Grade 2/Moderate	58 (48.3)	--
Grade 3/Severe	8 (6.7)	--
Grade 4/Life-threatening	0	--
Grade 5/Death	0	--
Subjects with AEs leading to treatment discontinuation	1 (0.8)	0.43
Subjects with AEs leading to treatment interruption	10 (8.3)	6.01
Subjects with grade 3/4/5 AEs	8 (6.7)	5.58
Subjects with related AEs	56 (46.7)	46.39
Subjects with serious AEs	13 (10.8)	7.30
Subjects with related serious AEs	1 (0.8)	0.43
Subjects with AEs leading to death	0	0

Source: Table 14.3.1.1

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

Notes: MedDRA version 25.1 was used. Events/100PY: number of events per 100 patient years (336 days=48 weeks per year) = number of events/total duration of treatment-emergent period for OLE study in 100PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category. 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. Subjects with grade 3/4/5 AEs include the 'Severe', 'Life Threatening' and 'Death' categories. If subjects only had one event which had missing severity, the subject was summarized in the "Missing" category.

Adverse Events

AEs that occurred in at least 20% of subjects are summarized by PT in Table 14.

Overall, AEs were generally consistent with common manifestations of CF disease or with common illnesses in CF subjects 6 years of age and older.

Table 14 Adverse Events Occurring in At Least 20% of Subjects by PT (OL Safety Set)

	Any ELX/TEZ/IVA N = 120	
PT	**n (%)**	**Events/100PY**
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with any AEs	118 (98.3)	707.80
COVID-19	70 (58.3)	33.50
Cough	62 (51.7)	70.01
Nasopharyngitis	54 (45.0)	49.39
Pyrexia	48 (40.0)	36.51
Headache	45 (37.5)	45.53
Upper respiratory tract infection	37 (30.8)	27.92
Oropharyngeal pain	32 (26.7)	21.90
Rhinitis	29 (24.2)	21.47
Abdominal pain	27 (22.5)	18.90
Vomiting	24 (20.0)	18.04

Source: Table 14.3.1.3
AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; PT: Preferred Term; PY: patient-years; TEZ: tezacaftor
Notes: MedDRA version 25.1 was used. A subject with multiple events within a category (Overall or PT) was counted only once in that category. Table is sorted in descending order of frequency of the Any ELX/TEZ/IVA column by PT.

CHMP comments

Almost all subjects had an AE, which is in line with previous studies of ELX/TEZ/IVA. No new events are observed when presented as at least 20% of the subjects above. In the table with all events (Table 14.3.1.2 CSR), however, anxiety was observed in 5 subjects (4.2%), and aggression and initial insomnia each in 2 subjects (1.7). Currently, except for depression, no psychiatric AEs are mentioned in the SmPC. However, as psychiatric events will be reviewed in the upcoming PSURs, this issue is currently not further pursued as part of this art 46 procedure.

Severity of Adverse Events

The majority of AEs were mild (43.3% of subjects) or moderate (48.3% of subjects) in severity. Eight (6.7%) subjects had severe AEs. No subjects had life-threatening AEs.

Grade 3/4/5 AEs are presented by SOC and PT in Table 15.Table 15Table 15 Grade 3/4/5 Treatment-emergent Adverse Events by System Organ Class and Preferred Term OL Safety Set

System Organ Class Preferred Term	Any ELX/TEZ/IVA N = 120 n (%)	Events/100PY
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with any Grade 3/4/5 TEAEs	8 (6.7)	5.58
Infections and infestations	3 (2.5)	2.15
Bacterial disease carrier	1 (0.8)	0.43
Infective pulmonary exacerbation of cystic fibrosis	1 (0.8)	0.43
Pneumonia pseudomonal	1 (0.8)	1.29
Gastrointestinal disorders	2 (1.7)	1.29
Constipation	1 (0.8)	0.86
Steatorrhoea	1 (0.8)	0.43
General disorders and administration site conditions	1 (0.8)	0.43
General physical health deterioration	1 (0.8)	0.43
Hepatobiliary disorders	1 (0.8)	0.86
Hepatic cirrhosis	1 (0.8)	0.43
Portal hypertension	1 (0.8)	0.43
Psychiatric disorders	1 (0.8)	0.43
Aggression	1 (0.8)	0.43
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0.43
Asthma	1 (0.8)	0.43

- MedDRA version 25.1.
- TEAE: Treatment-emergent adverse event.
- Subjects with Grade 3/4/5 TEAEs include the 'Severe', 'Life Threatening' and 'Death' categories.
- A subject with multiple events within a category (Overall, SOC or PT) is counted only once in that category.
- Table is sorted in descending order of frequency of the Any ELX/TEZ/IVA column by System Organ Class, and by Preferred Term within each System Organ Class.

CHMP comment

Grade 3/4/5 AEs were also classified as severe. All the Grade 3/4/5 AEs are generally consistent with common manifestations of CF disease or with common illnesses in CF subjects.

The hepatobiliary disorders will be further discussed below at Adverse Events of Special Interest (AESI).

Relationship of Adverse Events

One (0.8%) subject had AEs assessed by the investigator as related, and 55 (45.8%) subjects had AEs assessed by the investigator as possibly related.

Alanine aminotransferase increased and abdominal pain were the only related AEs with cut-off of ≥5%.

Table 16 Related AEs Occurring in At Least 5% of Subjects by PT (OL Safety Set)

Preferred Term	Any ELX/TEZ/IVA N = 120 n (%)
Subjects with any related AEs	56 (46.7)
Alanine aminotransferase increased	7 (5.8)
Abdominal pain	6 (5.0)

Source: Study 119 aCSR/Table 14.3.2.1

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

Notes: AEs were coded using MedDRA version 25.1. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted.

Deaths and SAE

There were no AEs leading to death

Other Serious Adverse Events

Thirteen (10.8%) subjects had at least 1 SAE. SAEs occurring in ≥1 subjects are presented by PT in Table 17. One (0.8%) subject had an SAE of steatorrhea that was assessed as related to study drug. SAEs were generally consistent with common CF manifestations and complications.

Table 17 SAEs Occurring in ≥ Subjects by SOC and PT (OL Safety Set)

	Any ELX/TEZ/IVA N = 120	
System Organ Class Preferred Term	n (%)	Events/100PY
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with any serious TEAEs	13 (10.8)	7.30
Infections and infestations	5 (4.2)	2.15
Infective pulmonary exacerbation of cystic fibrosis	2 (1.7)	0.86
Bacterial disease carrier	1 (0.8)	0.43
Pneumonia pseudomonal	1 (0.8)	0.43
Pneumonia staphylococcal	1 (0.8)	0.43
Gastrointestinal disorders	4 (3.3)	2.58
Constipation	1 (0.8)	0.86
Enteritis	1 (0.8)	0.43
Ileus paralytic	1 (0.8)	0.43
Intestinal obstruction	1 (0.8)	0.43
Steatorrhoea	1 (0.8)	0.43
Metabolism and nutrition disorders	2 (1.7)	0.86
Diabetes mellitus inadequate control	1 (0.8)	0.43
Weight gain poor	1 (0.8)	0.43
General disorders and administration site conditions	1 (0.8)	0.43
General physical health deterioration	1 (0.8)	0.43
Injury, poisoning and procedural complications	1 (0.8)	0.43
Head injury	1 (0.8)	0.43
Investigations	1 (0.8)	0.43
Blood glucose increased	1 (0.8)	0.43
Renal and urinary disorders	1 (0.8)	0.43
Haematuria	1 (0.8)	0.43

- MedDRA version 25.1.
- TEAE: Treatment-emergent adverse event.
- A subject with multiple events within a category (Overall, SOC or PT) is counted only once in that category.
- Table is sorted in descending order of frequency of the Any ELX/TEZ/IVA column by System Organ Class, and by Preferred Term within each System Organ Class.

CHMP comment

No new SAEs that could be attributed to the use of ELX/TEZ/IVA are observed. The SAEs were generally consistent with common CF manifestations and complications.

Adverse Events That Led to discontinuation of Study drug

Ten (8.3%) subjects prematurely discontinued treatment (Table 18). Of these 10 subjects, 1 (1.6%) subject had an AE of fatty stools. Most subjects (5.8%) discontinued because commercial drug became available for subject.

CHMP comment

The AE fatty stools leading to drug discontinuation is consistent with common manifestations of CF disease. No further action is required.

Adverse Events That Led to Interruption of Study Drug

Ten (8.3%) subjects experienced AEs leading to drug interruption.

Table 18 Treatment-emergent Adverse Events Leading to Drug Interruption by System Organ Class and Preferred Term OL Safety Set

System Organ Class Preferred Term	Any ELX/TEZ/IVA N = 120 n (%)	Events/100PY
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with TEAEs leading to treatment interruption	10 (8.3)	6.01
Investigations	3 (2.5)	2.15
Alanine aminotransferase increased	2 (1.7)	0.86
Aspartate aminotransferase increased	1 (0.8)	0.43
Blood bilirubin increased	1 (0.8)	0.43
Blood bilirubin unconjugated increased	1 (0.8)	0.43
Gastrointestinal disorders	2 (1.7)	1.29
Ileus paralytic	1 (0.8)	0.43
Intestinal obstruction	1 (0.8)	0.43
Steatorrhoea	1 (0.8)	0.43
Cardiac disorders	1 (0.8)	0.43
Tachycardia	1 (0.8)	0.43
Eye disorders	1 (0.8)	0.43
Photophobia	1 (0.8)	0.43
Metabolism and nutrition disorders	1 (0.8)	0.43
Weight gain poor	1 (0.8)	0.43
Nervous system disorders	1 (0.8)	0.43
Tremor	1 (0.8)	0.43
Psychiatric disorders	1 (0.8)	0.43
Anxiety	1 (0.8)	0.43
Skin and subcutaneous tissue disorders	1 (0.8)	0.43
Urticaria	1 (0.8)	0.43

- MedDRA version 25.1.
- TEAE: Treatment-emergent adverse event.
- A subject with multiple events within a category (Overall, SOC or PT) is counted only once in that category.
- Table is sorted in descending order of frequency of the Any ELX/TEZ/IVA column by System Organ Class, and by Preferred Term within each System Organ Class.

CHMP comment

Overall, the AEs leading to drug interruption are known AEs or common manifestations of CF disease. No further action is required.

Adverse Events of Special Interest

Elevated Transaminase Events

Overall, 11 (9.2%) subjects had at least 1 elevated transaminase event. All elevated transaminase events were mild or moderate in severity, and none were serious.

ALT or AST >3× and >5 × ULN occurred in 11 (9.2%) and 6 (5.0%) subjects, respectively. No subjects had ALT or AST >8 × ULN. No subjects had ALT or AST >3 × ULN with total bilirubin elevation >2 × ULN.

Elevated transaminase events are summarized in Table 19.

Table 19 Summary of Elevated Transaminase Events (OL Safety Set)

Category	Any ELX/TEZ/IVA N = 120 n (%)	Events/100PY
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with any Elevated Transaminase events	11 (9.2)	9.88
Alanine aminotransferase increased	11 (9.2)	6.44
Aspartate aminotransferase increased	6 (5.0)	3.44
Subjects with any events by maximum severity		
Grade 1/Mild	10 (8.3)	--
Grade 2/Moderate	1 (0.8)	--
Grade 3/Severe	0	--
Grade 4/Life-threatening	0	--
Grade 5/Death	0	--
Subjects with events leading to treatment discontinuation	0	0
Subjects with events leading to treatment interruption	2 (1.7)	1.29
Subjects with serious events	0	0
Subjects with related serious events	0	0
Subjects with events leading to death	0	0
Time-to-onset of first event (days)		
Subjects with event with complete start date	11	--
Mean (SD)	185.6 (229.3)	--
Median	120.0	--
Min, max	1, 668	--
Duration of events (days)		
Number of events	23	--
Number of events with duration	18	--
Mean (SD)	95.6 (106.3)	--
Median	54.0	--
Min, max	2, 339	--

Source: Table 14.3.2.8

AE: adverse event; AESI: Adverse events of special interest; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; OLE: open-label extension; PT: Preferred Term; PY: patient-years; TEZ: tezacaftor

Notes: Elevated transaminase events were coded using MedDRA version 25.1. 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 was counted only once in that category. When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing were counted. The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date, with the first dose date of study drug in the OLE study as the reference. Preferred Terms are sorted by alphabetical order. If subjects only had one event which had missing severity, the subject was summarized in the "Missing" category.

At request of CHMP also all hepatic AEs observed in Study 119 are summarised (Table 20).

A total of 6 subjects had 7 events of hepatobiliary disorders, 2 of whom also had elevated transaminase events. Of the 6 subjects, 5 had a history of CF hepatic disease or previous elevations of transaminase and/or bilirubin levels.

The reported events occurred from 1.5 months to 1 year after ELX/TEZ/IVA initiation. None of the events led to change in study drug dosing. Of the 2 events considered possibly related to ELX/TEZ/IVA

treatment by the investigator, both were ongoing at the end of the study participation without change to study drug dosing.

Table 20 Summary of Hepatic AEs by PT (OL Safety Set)

Preferred Term	Any ELX/TEZ/IVA N = 120 n (%)
Alanine aminotransferase increased	11 (9.2)
Aspartate aminotransferase increased	6 (5.0)
Hepatic cirrhosis	3 (2.5)
Hepatic steatosis	1 (0.8)
Hyperbilirubinaemia	1 (0.8)
Nodular regenerative hyperplasia	1 (0.8)
Portal hypertension	1 (0.8)

Source: Study 119 aCSR/Table 14.3.1.2

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

Notes: AEs were coded using MedDRA version 25.1. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

CHMP comment

Overall, the elevated transaminase events are in line with previous studies.

Regarding the hepatic AEs, most subjects had already a medical history of CF hepatic disease or liver function test fluctuations. Only 1 subject did not have a history of CF hepatic disease, but the new developed hepatic steatosis was considered unlikely related to study drug by the investigator. Therefore, these new cases have not lead to new information.

As a warning to be cautious with use in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) is already included in the SmPC, a change of the SmPC is not warranted as the information of these new cases has not lead to new information.

Rash Events

Rash events were considered an AESI and occurred in 13 (10.8%) subjects. All rash events were mild or moderate in severity, and none were serious. No subject had a rash event that led to treatment discontinuation, and 1 (0.8%) subject had a rash event that led to treatment interruption. (Table 21)

Overall, 10 (14.5%) of 69 female subjects and 3 (5.9%) of 51 male subjects had rash events.

Table 21 Summary of Rash Events (OL Safety Set)

Category	Any ELX/TEZ/IVA N = 120 n (%)	Events/100PY
Total duration of OL treatment-emergent period in 100 PY	--	2.33
Subjects with any events	13 (10.8)	6.87
Dermatitis	2 (1.7)	0.86
Rash	4 (3.3)	1.72
Rash pruritic	3 (2.5)	1.29
Urticaria	5 (4.2)	2.58
Vasculitic rash	1 (0.8)	0.43
Subjects with any events by maximum severity		
Grade 1/Mild	10 (8.3)	--
Grade 2/Moderate	3 (2.5)	--
Grade 3/Severe	0	--
Grade 4/Life-threatening	0	--
Grade 5/Death	0	--
Subjects with events leading to treatment discontinuation	0	0
Subjects with events leading to treatment interruption	1 (0.8)	0.43
Subjects with serious events	0	0
Subjects with related serious events	0	0
Subjects with events leading to death	0	0
Time-to-onset of first event (Days)		
Subjects with event with complete start date	12	--
Mean (SD)	121.8 (216.3)	--
Median	45.0	--
Min, max	2, 656	--
Duration of events (Days)		
Number of events	16	--
Number of events with duration	12	--
Mean (SD)	16.9 (30.7)	--
Median	5.5	--
Min, max	1, 105	--

Source: Table 14.3.2.9

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; OLE: open-label extension; PT: Preferred Term; PY: patient-year; 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 of subjects with events, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing were counted. The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date, with the first dose date of study drug in the OLE study as the reference. Preferred Terms are sorted by alphabetical order. If subjects only have 1 event which has missing severity, then the subject was summarized in the "Missing" category.

CHMP comment

Overall, the AEs leading to drug interruption are known AEs or common manifestations of CF disease. Only information is provided regarding the related SAEs, while also information regarding related AEs of rash would have been expected. However, because adequate information regarding rash is already included in the SmPC in section 4.4 and section 4.8, no further information is requested.

Clinical Laboratory Evaluation

Haematology

There were no trends observed in haematology parameters.

Overall, AEs related to haematology were infrequent. None of the AEs related to haematology were serious or led to treatment discontinuation.

Chemistry

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

Liver Function Tests

The majority of subjects had ALT and AST values that remained ≤ 3 x ULN (Table 22). Eleven (9.2%) subjects had ALT or AST >3 x ULN and 6 (5.0%) subjects had ALT or AST >5 x ULN.

No subjects had ALT or AST >8 x ULN. No subjects had ALT or AST >3 x ULN with total bilirubin elevation >2 x ULN.

Overall, the data related to transaminase elevations were consistent with prior experience.

Table 22 Threshold Analysis of LFT Chemistry Parameters (OL Safety Set)

Parameter Subjects with Non-missing Post-TC-Safety-Baseline Data Post-TC-Safety-Baseline Threshold Analysis Criteria, n (%)	Any ELX/TEZ/IVA N = 120
ALT (U/L)	
Total, N1	120
>3 × ULN	11 (9.2)
>5 × ULN	6 (5.0)
>8 × ULN	0
AST (U/L)	
Total, N1	120
>3 × ULN	3 (2.5)
>5 × ULN	0
>8 × ULN	0
ALT (U/L) or AST (U/L)	
Total, N1	120
(ALT>3 × ULN) or (AST>3 × ULN)	11 (9.2)
(ALT>5 × ULN) or (AST>5 × ULN)	6 (5.0)
(ALT>8 × ULN) or (AST>8 × ULN)	0
Total bilirubin (µmol/L)	
Total, N1	120
>ULN to ≤1.5 × ULN	6 (5.0)
>1.5 × to ≤2 × ULN	3 (2.5)
>2 × to ≤3 × ULN	0
>3 × to ≤10 × ULN	1 (0.8)
>10 × ULN	0

Source: Table 14.3.4.2

ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; N1: number of subjects with at least 1 non-missing measurement during the treatment-emergent period; OL: open-label; OLE: open-label extension; TC: triple combination; TEZ: tezacaftor; ULN: upper limit of normal

Notes: TC safety baseline was 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 during the parent study) or the first dose of study drug in the OLE study (if the subject did not actually receive at least one dose of ELX/TEZ/IVA during the parent study). Within each parameter, a subject was counted in all applicable post-TC-safety-baseline categories based on the worst assessment during the treatment-emergent period; percentage is n/N1. Criteria involving 2 LFT parameters may have been determined by assessments at different visits during the treatment-emergent period.

CHMP comment

Overall, the elevated transaminase events are in line with previous studies. See also section AESI.

Creatinine Kinase

There were no trends observed in CK concentration levels.

Overall, 2 (1.7%) subjects had CK >5 x ULN to ≤10 x ULN, and 1 (0.8%) subject had CK >10 x ULN. AEs of blood creatine phosphokinase increased occurred in 2 (1.7%) subjects, and no subject discontinued treatment due to an AE of blood creatine phosphokinase increased. Both AEs of blood creatine phosphokinase increased were mild in severity and neither led to treatment interruption.

CHMP comment

Overall, the elevated CK events are in line with previous studies. Adequate information regarding rash is already included in the SmPC in section 4.8 of the SmPC.

Coagulation

There were no trends observed in coagulation parameters.

Overall, AEs related to coagulation parameters were infrequent. None of the AEs related to coagulation parameters were serious or led to treatment interruption or discontinuation.

Urinalysis

There were no trends in urinalysis results. AEs related to urinalysis were infrequent.

One subject had an SAE of haematuria that was assessed by the investigator as not related to study drug and resolved without treatment.

No other urinalysis AEs were serious or led to treatment interruption or discontinuation.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

There were no trends observed in the vital signs parameters.

The mean (SD) triple combination (TC) safety baseline values were 103.3 (9.4) mm Hg for systolic blood pressure (SBP) and 64.0 (8.6) mm Hg for diastolic blood pressure (DBP). Mean SBP and DBP were variable over time. At Week 96, the mean increase in SBP was 3.2 mm Hg and the mean increase in DBP was 1.0 mm Hg.

Overall, AEs related to vital signs parameters were infrequent. One subject had an SAE of weight gain poor that led to treatment interruption, was assessed by the investigator as unlikely related to study drug and resolved with treatment. No other AEs related to vital signs parameters were serious or led to treatment interruption or discontinuation.

Overall, the vital signs data were consistent with prior experience.

Pulse Oximetry

There were no trends in pulse oximetry.

Electrocardiograms

There were no trends observed in ECG parameters.

AEs related to ECG findings or relevant cardiac disorders were infrequent. None of the AEs related to ECG findings or relevant cardiac disorders led to treatment discontinuation or interruption.

Overall, the ECG data in were consistent with prior experience.

Table 23 Threshold Analysis of ECGs During the Treatment-emergent Period OL Safety Set

Parameter Subjects with Non-missing Post-TC-Safety-Baseline Data Post-TC-Safety-Baseline Threshold Analysis Criteria, n (%)	Any ELX/TEZ/IVA N = 120
ECG mean heart rate (beats/min)	
Total, N1	120
Bradycardia	
≤50 beats/min	1 (0.8)
Tachycardia	
≥140 beats/min	0
PR interval, single beat (msec)	
Total, N1	120
≥220 msec and increase from baseline ≥20 msec	0
QRS duration, single beat (msec)	
Total, N1	120
≥120 msec	1 (0.8)
QTcF interval, single beat (msec)	
Total, N1	120
>450 msec (male) or >470 msec (female)	0
≥500 msec	0
Increase from baseline 30 to 60 msec	22 (18.3)
Increase from baseline >60 msec	1 (0.8)

- 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 during the parent study) or the first dose of study drug in the OLE study (if the subject did not actually receive at least one dose of ELX/TEZ/IVA during the parent study).
- N1: number of subjects with at least one non-missing measurement during the treatment-emergent period.
- n (%): n is the number of subjects in the post-TC-safety-baseline category; within each parameter, a subject is counted in all applicable post-TC-safety-baseline categories based on the worst assessment during the treatment-emergent period; percentage is n/N1.

CHMP comment

Generally, the threshold analysis of the ECGs showed changes that were observed in only 1 subject. Although the observations of increases of the QTcF interval might have given concerns, this is accepted. During the initial MAA a dedicated QTc study with elexacaftor (Study 009) was performed that did not show prolongation of QTc interval.

Physical Examinations

Physical examination (PE) findings were not listed. Clinically relevant PE findings were reported as AEs.

Ophthalmologic Examinations

Ophthalmologic examination results are presented for subjects <18 years of age on the date of signing the informed consent form (ICF) or assent form in the parent study.

Three (2.5%) subjects had an AE of cataract and one (0.8%) subject had an AE of lenticular opacities. All AEs were mild and nonserious and did not lead to change in study drug dosing.

3.1.3. Discussion on clinical aspects

Study 119 was a Phase 3b, multicenter, open-label study for subjects who completed the parent study (VX19-445-116 [Study 116]). Study 119 consisted from a Treatment Period of 96 weeks and a 4 week Safety Follow-up period.

The primary objective of study 119 is to evaluate the long-term safety and tolerability of ELX/TEZ/IVA in subjects with CF who are heterozygous for the F508del mutation a Minimal Function Mutation (F/MF)

Eligible subjects six years of age and older were enrolled who participated in Study 116 and who completed study drug treatment in the parent study. Subjects had to fulfil the main inclusion criteria of Study 116 i.e., ppFEV1 ≥ 70% or $LCI_{2.5}$ ≥7.5, indicative for a impairment of the small airways.

The dosing was according to the approved dosing in the SmPC. The rules for concomitant stable CF medication, restriction of CYP3A inducers and CYP3A inhibitors were all acceptable. Subjects remained on a stable CF medication that the subject had been following for at least 28 days before Day 1. Co-administration of ELX/TEZ/IVA with moderate and strong CYP3A inducers and inhibitors was restricted in this study, although dosing modification of CYP3A inhibitors are currently described in the approved SmPC. Nevertheless, the same restrictions were applied in the pivotal studies and these more strict rules are considered acceptable for the purpose of a study.

Outcome measures

Multiple outcomes were included. As efficacy was a secondary objective, no primary endpoint is defined. The main secondary outcomes are SwCl, LCI2.5, ppFEV1 CFQ-R respiratory domain. Sweat chloride, although strictly a pharmacodynamic parameter, is important for measuring the effect of a modulator on the underlying pathology. Pulmonary function tests (LCI2.5, ppFEV1) are considered important to measure an effect on one of the most important affected organs in CF. CFQ-R measures the quality of life. Thus, all parameters inform about a different aspect of CF and are considered important for measuring the efficacy of a CF modulator.

Safety measures are standard measurements plus, ophthalmologic examinations (OE; subjects <18 years of age).

Statistics

As study 119 was an open-label single arm study, randomization as well as blinding is not possible because all subjects will be treated identically. Overall sample size is low for detecting uncommon safety signals.

For the efficacy analyses, parent study baseline was used to calculate the change from baseline for efficacy analyses unless otherwise specified. Parent study baseline was defined as the most recent non-missing measurement collected before the first dose of study drug in the parent study. The principle to define the analyses sets for safety and efficacy based on when and whether ELX/TEZ/IVA was used, is understood.

Analysis of repeated measurements was done with mixed model (MMRM). For outcomes other than LCI2.5 (e.g., SwCl), the baseline of the outcome was not included in the model, but instead the baseline of LCI2.5 was used.

Changes in conduct

Generally, the changes made in the protocol were acceptable.

There were four subjects with IPDs during the Treatment Period; none of which are considered to have impacted results to a large extent.

Efficacy Results

A total of 110 (91.7%) of the 120 subjects who received at least 1 dose of ELX/TEZ/IVA completed treatment and the study. The most common reason for discontinuation of treatment was commercial drug became available for the subject (7 [5.8%] subjects).

Demographics and baseline characteristics were generally similar between groups across the parent studies. The mean age at parent study baseline was 9.1 years, and 57.5% of the subjects were female. The majority of subjects (72.5%) were White.

A population with mildly impaired lung function (ppFEV1 89.4%, $LCI_{2.5}$ 9.98) and high SwCl (102.7 mmol/L) was included. Nutritional scores were low e.g., BMI (16.19) and BMI z-score (- 0.28) at baseline.

Outcomes

Subjects from the placebo arm of the parent study showed efficacy improvements that were generally consistent with the parent study when beginning ELX/TEZ/IVA in the OLE study. The improvements were maintained through the rest of this OLE study. For the ELX/TEZ/IVA arm, the initial improvements were maintained throughout the parent study and OLE study.

The LS mean change from parent study baseline in SwCl was -57.3 (95% CI: -61.6, -52.9) and -57.5 (95% CI: -62.0, -53.0) for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively. These changes are relevant, and they demonstrate the effect of a modulator on the underlying pathology. Overall, the effect was maintained over the period of parent Study 116 (24 weeks) and OLE Study 119 (96 weeks).

The effect on the lung is demonstrated by an improvement of $LCI_{2.5}$, i.e. a LS mean change from parent study baseline of -1.74 (95% CI: -2.09, -1.38) and -2.35 (95% CI: -2.72, -1.97) for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively. Also ppFEV1 improved as demonstrated by LS mean change from parent study baseline of 6.1 (95% CI: 2.6, 9.7) and 6.9 (95% CI: 3.2, 10.5) for subjects from the placebo and ELX/TEZ/IVA arms of the parent study, respectively. Again, effect that was obtained in Study 116, was maintained over the period of Study 119.

Quality of life improved as well, as demonstrated by the improvement in CFQ-R RD, in the ELX/TEZ/IVA arm with 6.6 point and in placebo arm in parent study and 2.6 in the ELX/TEZ/IVA arm of the parent study. Although the improvement is not as high as seen before, it is still considered relevant especially in the placebo arm of study 116.

Missing data at week 96 were limited for CFQ-R RD, but more substantial for sweat chloride and $LCI_{2.5}$ (up to 20%) and pronounced for ppFEV1 (above 30%). Considering the reasons for missingness, for most of the missing data it cannot be fully assumed that they are not-informative of an inferior outcome. Nevertheless, taking into account the actual results that are generally consistent with the pivotal studies of Kaftrio and the pattern of the missingness, it seems that the high number of missing data did not impact the reliability of the results. Furthermore, it is not uncommon that missing data are higher in a long-term safety study, especially considering part of the study was during the COVID period. Therefore, considering the objective of the study this not further pursued.

Modified MMRM analysis using the relevant parameter at baseline were provided. The estimates and 95% CI are generally similar between the original planned analysis and the analyses correcting for the baseline of the outcome. Although some small differences were observed for both groups placebo-ELX/TEZ/IVA and ELX/TEZ/IVA-ELX/TEZ/IVA, the results in all parameters are clinically relevant.

The efficacy results of the secondary endpoint analyses are generally comparable to effects observed in the pivotal authorisation study in adults and adolescents, Study 102, and to the authorisation study in children 6 through 11 years, Study 106.

Safety

ELX/TEZ/IVA was generally safe and well tolerated for 96 weeks of treatment in subjects 6 years of age and older, as demonstrated by the low number of severe AE, related SAEs and low number of discontinuations due to a AE.

Although the proportion of subjects with at least 1 adverse event (AE) was high (98.3%), most subjects had AEs that were mild or moderate in severity. Eight (6.7%) subjects had severe AEs, while there were no life-threatening AEs or deaths.

The most common AEs (occurring in ≥20% of subjects) were generally consistent with common manifestations of CF disease or with common illnesses in CF subjects 6 years of age and older. No new AEs with a high frequency were observed. The number of patients is, however, quite low to detect new AEs. Neither no new information of related AEs was found. Alanine aminotransferase increased and abdominal pain were the only related AEs that occurred above a cut-off of ≥5%.
Thirteen (10.8%) subjects had SAEs, of whom only one (0.8%) subject had an SAE of steatorrhoea that was assessed as related to study drug. Two (1.7%) subjects had an SAE of infective PEx of CF. No other SAE occurred in more than 1 subject.

Discontinuation was low, as only one (0.8%) subject discontinued study drug due to steatorrhea. Ten (8.3%) subjects interrupted study drug due to AEs.

Elevated transaminase events were considered an AE of special interest (AESI) and occurred in 11 (9.2%) subjects. All elevated transaminase events were mild or moderate in severity, and none were serious. ALT or AST >3 and >5 × ULN occurred in 11 (9.2%) and 6 (5.0%) subjects, respectively. No subjects had ALT or AST >8 × ULN. No subjects had ALT or AST >3 × ULN with total bilirubin elevation >2 × ULN. Overall, reported elevated transaminases are in line with previous observations. An adequate warning and recommendation for regular assessment is already included in the SmPC. In addition to the events of elevated transaminases, 6 subjects had 7 events of hepatobiliary disorders. Most of subjects had already a medical history of CF hepatic disease or liver function test fluctuations. The information of these new cases does not lead to new information that warrants a change of the SmPC.

Rash was also considered an AESI. Rash occurred in 13 (10.8%) subjects. All rash events were mild or moderate in severity, and none were serious. A warning regarding rash is already included in the SmPC in section 4.4 and the frequency of very common in section 4.8. Thus, no further action is required.

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

4. CHMP overall conclusion and recommendation

Study 119 was the open-label study following parent Study 116.

Treatment with ELX/TEZ/IVA resulted in maintained improvement of efficacy parameters from baseline for subjects that already received ELX/TEZ/IVA in Study 116. Subjects from the placebo arm in Study 116 achieved the same improvements as the subjects from the ELX/TEZ/IVA arm in Study 116.

ELX/TEZ/IVA was generally safe and well tolerated for 96 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 adults and adolescents (Study 102 and Study 103) as well as in children 6 through 11 years (Study 106).

The benefit-risk evaluation of Kaftrio remains positive.

☒ **Fulfilled:**

5. 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 provide the rules for concomitant medication e.g., stable CF medication, restriction of CYP3A inducers and CYP3A inhibitors
2. Regarding the protocol versions, the applicant is asked to explain the differences found between the CSR body and Appendix 16.1.1:
   a. the amendments made in version 2 and version 3
   b. whether amendments made in version 2 and were also included in versions 1.2, 1.3 and 1.4 given the latter dates of these versions.
3. Version 1.3 DE included additional exclusion criteria. The applicant is requested to provide the details of these changes instead of the current general description in order to assess the impact.
4. In parent study 116, LCI2.5 at baseline (and weight) were used as covariates in the CFQ, ppFEV1, sweat chloride (and LCI2.5) analyses. It should be clarified whether that was the case in this OLE study 119 as well. If so, original analysis results and those with the outcome at baseline as covariate instead should be presented side by side to show the impact.
5. Already in parent study 116 (24 weeks), but more pronounced in this OLE study 119 (week 96), there is substantial missing data at the last time point (week 96). Although limited for CFQ-R RD (~10%), it is more substantial for LCI2.5 and sweat chloride (up to 20%) and pronounced for ppFEV1 (above 30%). Missing data patterns should be presented. Informed by these patterns, the impact of missingness on the change to week 96 analysis should be discussed, in particular in view of the intended target of estimation (ICH E9 R1).
6. Related AEs are presented in an inconvenient table. The MAH is requested for a table containing related AE Adverse Events by Preferred Term OL Safety Set with cut-off of ≥5%.
7. In order to complete the evaluation of risk regarding hepatic events, the applicant is requested to discuss all reported hepatic AEs instead of solely the elevated transaminase events.

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

6. MAH responses to Request for supplementary information

Question 1

The applicant is requested to provide the rules for concomitant medication e.g., stable CF medication, restriction of CYP3A inducers and CYP3A inhibitors

Summary of the applicant's response

The rules for concomitant medication specified in the Study 445-119 (Study 119) protocol in Section 9.4/Table 9-2 is provided below as Table 1 in its entirety.

Additionally, Section 9.5 of the protocol provides information regarding use of prior and concomitant medications, including the use of a stable cystic fibrosis (CF) treatment regimen. In brief:

"Subjects should remain on a stable treatment regimen for their CF through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before Day 1. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:

- Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule.
- Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study."

Table 24 Prohibited medications

	Timing of Restriction		
Medication	**Start of Restriction**	**End of Restriction**	**Rationale**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers of CYP3A and moderate and strong inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, are prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drugs in the parent study and this study	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

CYP: cytochrome P450; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

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

Assessment of the response of the applicant

The applicant refers to the protocol of study 119 for the rules of concomitant medication. The applied rules are as in the precursor Study 116.

The rules for concomitant stable CF medication were all acceptable. Subjects remained on a stable CF medication that the subject had been following for at least 28 days before Day 1. Co-administration of ELX/TEZ/IVA with moderate and strong CYP3A inducers and inhibitors was restricted in this study, although dosing modification of CYP3A inhibitors are currently described in the approved SmPC. Nevertheless, the same restrictions were applied in the pivotal studies and these more strict rules are considered acceptable for the purpose of a study.

Conclusion

Issue resolved

***Question* 2**

Regarding the protocol versions, the applicant is asked to explain the differences found between the CSR body and Appendix 16.1.1:

- ***a. the amendments made in version 2 and version 3***
- ***b. whether amendments made in version 2 and were also included in versions 1.2, 1.3 and 1.4 given the latter dates of these versions.***

Summary of the applicant's response

Table 9-2 in the abbreviated clinical study report (aCSR) body summarizes Study 119 protocol versions 1.0, 1.1 DE (Germany), 1.2 FR (France), and 1.3 DE, which were all the versions of the protocol that were submitted to health authorities. Appendix 16.1.1 includes these protocol versions, as well as version 1.4 ES (Spain), which was not implemented in Spain given that commercial drug was made available to study subjects prior to generation of this amendment.

Appendix 16.1.1 also includes all relevant versions of the COVID-19 protocol addendum that outlined additional measures taken during the COVID-19 pandemic for Vertex CF clinical trials (including Study 119). This COVID-19 protocol addendum was not study-specific, but rather applied to a number of Vertex clinical trials that were ongoing during the pandemic.

Table 2 below summarizes the changes made in all versions of the COVID-19 protocol addendum. Please note that all measures in prior versions of the addendum were captured in subsequent versions (i.e., changes in version 1.0 applied to versions 2.0 and 3.0, changes in version 2.0 applied to version 3.0).

The COVID-19 protocol addendum was applicable to all versions of the Study 119 protocol.

Table 25 Summary of changes in CF Clinical Study protocol Addendum During the COVID-19 Pandemic

Protocol Change	Rationale for Change
Addendum Version 3.0, dated 29 July 2020	
Assessments Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19.
Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.

Addendum Version 2.0, dated 15 May 2020	
Assessments Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices. Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files.	To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel. *Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.*
Addendum Version 1.0, dated 24 April 2020	
Consenting of Subjects ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator. Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable.	To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety.
Study Drug Shipping Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex. Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations.	To ensure subjects can continue treatment with study drug without interruption while ensuring their safety. To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol.
In-home Visits and/or Telephone Contact Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits.	To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel.
Safety Assessments and Reporting Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation: • vital signs • pulse oximetry • height/length/stature • weight • physical examination (complete or abbreviated) • pregnancy test (serum or urine) • urinalysis • blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation). Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits. Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site. In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following: • AEs • signs and symptoms/systems for CF • medications • planned or unplanned hospitalizations for CF • study drug administration • outcomes related to PEx • outcomes related to antibiotic treatment Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol.	To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel. To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol.

Efficacy and Other Assessments Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation. In-home Spirometry Assessment A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed. Patient Reported Outcome CFQ-R questionnaires may be provided to subjects (electronically or post mail) to be completed at home as indicated per protocol. Subjects will return these questionnaires to the site via post mail. Other Assessments • ECGs • sweat chloride • blood samples for *CFTR* genotype testing, IRT, PK, FSH, inflammatory mediator, biomarkers, and vitamin levels • fecal samples for FE-1, fecal calprotectin, and other markers of intestinal inflammation • other patient reported outcomes (e.g., TSQM, SF-12)	To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety.
Remote Monitoring Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints.	To allow for review of key data to inform on the safety of subjects receiving treatment. To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel.

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; FE-1: fecal elastase-1; FSH: follicle-stimulating hormone; ICF: informed consent form; IRT: immunoreactive trypsinogen; LFT: liver function test; PEx: pulmonary exacerbation; PK: pharmacokinetic; SAE: serious adverse event; SF-12: 12-Item Short Form Health Survey; TSQM: Treatment Satisfaction Questionnaire for Medication

Assessment of the response of the applicant

The applicant has attempted to explain the versions of the protocols.

In the document VX20-445-119-16-1-1, the date of Protocol Version 1.0 is 26 June 2020. With the response, the date of addendum 1.0 is 24 April 2020. The date of Protocol Version 3.0 is 29 July 2020 that replaces Version 2.0, dated 15 May 2020. Version 2.0 is not included in the documentation. The dates are the same dates as in the response for date of addendum 3.0 and addendum 2.0. Thus, it seems that the date of protocol version 1.0 in the document VX20-445-119-16-1-1, is incorrect.

The applicant explained further that all measures in prior versions of the addendum were captured in subsequent versions (i.e., changes in version 1.0 applied to versions 2.0 and 3.0, changes in version 2.0 applied to version 3.0). the numbering of the country specific versions suggest that they were based on version 1, i.e., Version 1.2FR September 2020, Version 1.3DE 3 February 2021, Version 1.4ES 9 September 2022. The dates of these versions lay behind the date of version 3.0. The applicant did not explain whether the amendments in versions 2.0. and 3.0 were also implemented in the country specific as was specifically requested in subquestion b.

Despite the confusion regarding the dates and the country-specific version numbering, the provided information in table 2 (and table 3 in question 3) is sufficient.

Conclusion

Issue not further pursued.

***Question* 3**

Version 1.3 DE included additional exclusion criteria. The applicant is requested to provide the details of these changes instead of the current general description in order to assess the impact.

Summary of the applicant's response

At the request of the German health authority (BfArM), protocol version 1.3 DE included additional exclusion criteria to more closely align with those in the parent study protocol (Study VX19-445-116 [Study 116]). The changes in bold in Table 3 were made to the exclusion criterion of Study 119.

Version 1.0 of the Study 119 protocol, which was submitted to all study countries, did not contain any of these changes. Vertex confirms that the disparity in these exclusion criteria did not prevent any subjects from enrolling in Study 119, as all subjects in Study 116 rolled over to Study 119, except for 1 subject who discontinued Study 116 due to an adverse event (AE) of rash.

Table 26 Summary of changes in exclusion criterion in Studies 116 and 119

Exclusion Criterion in Parent Study 116 Protocol Version 1.1 DE	Amended Exclusion Criterion in Study 119 Protocol Version 1.3 DE
1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following: • Clinically significant liver cirrhosis with or without portal hypertension • Solid organ or hematological transplantation • Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator • Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)	1. History of any comorbidity that~~, in the opinion of the investigator,~~ might confound the results of the study or pose an additional risk in administering study drug to the subject. **This includes, but is not limited to, the following:** • **Clinically significant liver cirrhosis with or without portal hypertension** • **Solid organ or hematological transplantation** • **Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates** • **Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)**
N/A	2. History of drug intolerance in the parent study that would pose an additional risk to the subject ~~in the opinion of the investigator~~ (e.g., subjects with a history of allergy or hypersensitivity to the study drug).
8. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-2.	5. **Use of restricted medication as defined in Table 9-2, unless subject is on a study drug interruption at the time of rollover.**
10. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.	6. **The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.**

Assessment of the response of the applicant

The applicant explained the amendment in the exclusion criteria in the country specific Version of DE. Although the changes could have led to disparity between the included subjects, the applicant confirmed that the changed exclusion criteria did not prevent any subjects to roll over.

Conclusion

Issue resolved

***Question* 4**

In parent study 116, LCI2.5 at baseline (and weight) were used as covariates in the CFQ, ppFEV1, sweat chloride (and LCI2.5) analyses. It should be clarified whether that was the case in this OLE study 119 as well. If so, original analysis results and those with the outcome at baseline as covariate instead should be presented side by side to show the impact.

Summary of the applicant's response

Parent study baseline LCI2.5 and weight at screening of the parent study were included as covariates in the Study 119 original mixed-effects model for repeated measures (MMRM) analyses for all efficacy endpoints. The models in Study 119 were designed to be consistent with the parent Study 116 models to allow direct comparison of the parent study results to the Study 119 results. In parent Study 116, the randomization factors included LCI2.5 and weight, and the MMRM model covariates were baseline LCI2.5 and weight at screening (<30 versus ≥30 kg).

Modified MMRM analyses are provided as requested (Table 4). The MMRM analyses were modified by adding the baseline value of the outcome itself as an additional covariate for the continuous endpoints sweat chloride (SwCl), percent predicted forced expiratory volume in 1 second (ppFEV1), and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score.

Overall, the results of the modified MMRM analyses were generally consistent with the original analyses (95% confidence intervals were largely overlapped).

Table 27 original and modified MMRM analyses: Study 119 OL-FAS

		OL Week 96			
		Original MMRM		Modified MMRM	
Analysis	Statistic	PBO in Study 116 N = 61	ELX/TEZ/IVA in Study 116 N = 59	PBO in Study 116 N = 61	ELX/TEZ/IVA in Study 116 N = 59
Absolute change from parent study baseline in SwCl (mmol/L) at OL Week 96	n	52	46	52	46
	LS mean (SE)	-57.3 (2.2)	-57.5 (2.3)	-57.3 (2.0)	-57.5 (2.0)
	95% CI of LS mean	(-61.6, -52.9)	(-62.0, -53.0)	(-61.2, -53.4)	(-61.5, -53.4)
Absolute change from parent study baseline in ppFEV$_1$ (percentage points) at OL Week 96	n	41	38	41	38
	LS mean (SE)	6.1 (1.8)	6.9 (1.9)	5.1 (1.6)	8.1 (1.7)
	95% CI of LS mean	(2.6, 9.7)	(3.2, 10.5)	(1.9, 8.4)	(4.8, 11.4)
Absolute change from parent study baseline in CFQ-R RD score (points) at OL Week 96	n	56	54	56	54
	LS mean (SE)	6.6 (2.1)	2.6 (2.1)	5.4 (1.8)	4.3 (1.8)
	95% CI of LS mean	(2.5, 10.8)	(-1.6, 6.8)	(1.8, 8.9)	(0.6, 7.9)

Sources: Study 119 aCSR/Tables 11-1, 11-3, and 11-4, and Ad hoc Tables 14.2.1.2.1, 14.2.3.2.1, and 14.2.4.2.1

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; 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; OL: open-label; PBO: placebo; 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 (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study. For the OLE, the modified 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 $LCI_{2.5}$, parent study baseline values (for each respective endpoint), and weight at screening (<30 versus ≥30 kg) of the parent study 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 of the applicant

The rationale to have a consistent analysis to that of the parent study is understood. As noted in earlier assessments, the choice in the parent study to have the analysis not correcting for baseline of the outcome is unusual. Estimates and 95% CI are generally similar between the original planned analysis and the analyses correcting for the baseline of the outcome. Although some differences were observed for both groups placebo-ELX/TEZ/IVA and ELX/TEZ/IVA - ELX/TEZ/IVA, the results in all parameters are clinically relevant.

Conclusion

Issue resolved.

***Question* 5**

Already in parent study 116 (24 weeks), but more pronounced in this OLE study 119 (week 96), there is substantial missing data at the last time point (week 96). Although limited for CFQ-R RD (~10%), it is more substantial for LCI2.5 and sweat chloride (up to 20%) and pronounced for ppFEV1 (above 30%). Missing data patterns should be presented. Informed

by these patterns, the impact of missingness on the change to week 96 analysis should be discussed, in particular in view of the intended target of estimation (ICH E9 R1).

Summary of the applicant's response

Similar to findings in Study 116, analyses of missing data patterns support Vertex's assumption that data are missing at random. The major reasons for missing data were either study discontinuation or assessments not meeting criteria that are independent of treatment. Therefore, Vertex assesses that there is little impact of missingness on efficacy conclusions. Additional details are provided below.

Of the 10 subjects who discontinued the study, 7 subjects discontinued due to commercial drug availability, 2 subjects withdrew consent (not due to AE), and 1 subject discontinued due to AE. Vertex considers the missing-at-random assumption reasonable for these subjects because discontinuation due to commercial drug availability and withdrawal of consent (not due to AE) are: 1) independent of the efficacy data, 2) distinguished from discontinuation of treatment, and 3) not considered as intercurrent events per ICH E9 R1.

At the open-label (OL) Week 96 analysis visit,

- Among the 22 (18.3%) subjects missing SwCl, reasons for missing data were study discontinuation (n = 9), other or unknown (n = 8, which includes 1 subject who discontinued due to commercial drug availability, but SwCl was not measured at their Early Termination of Treatment [ETT] Visit), and assessment done but not meeting criteria due to volume <15 µL (n = 5) (Table 28).

Table 28 Summary of Data Availability for Absolute Change from Baseline in Sweat Chloride at Each Visit up to OL Week 96 OL Full Analysis Set

	Parent Study Baseline	OL Week 4	OL Week 8	OL Week 16	OL Week 24	OL Week 48	OL Week 72	OL Week 96
Data available	120	113	115	116	111	105	111	98
Data missing	0	7	5	4	9	15	9	22
Reason for missing								
Study discontinuation	0	0	0	0	1	2	4	9
Assessment done but not meeting criteria [a]	0	5	5	2	3	9	2	5
COVID-19 pandemic [b]	0	0	0	1	1	2	0	0
Other or unknown	0	2	0	1	4	2	3	8
Missing baseline [c]	n/a	0	0	0	0	0	0	0

- Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study.
- [a]: any results reported as having volume <15 µL, or sweat chloride values <10 mmol/L or >160 mmol/L were considered missing for analysis purposes.
- [b]: missing due to COVID-19 pandemic is defined as (1) assessment not done and "Visit conduct was impacted by COVID-19" was recorded in the clinical data base or (2) "Visit was not conducted (in any format) due to COVID-19" was recorded in clinical data base.
- [c]: the post-baseline value is available but change from baseline is missing due to missing baseline. Only applicable to post baseline visits.

- Among the 16 (13.3%) subjects missing LCI2.5, reasons for missing data were study discontinuation (n = 9, which excludes 1 subject with LCI2.5 measured at their ETT Visit), assessment done but only one or no accepted replicate (n = 5), COVID-19 pandemic (n = 1), and other or unknown (n = 1) (Table 29).

Table 29 Summary of Data Availability for Absolute Change from Baseline in LCI2.5 at Each Visit up to OL Week 96 OL Full Analysis Set

	Parent Study Baseline	OL Week 4	OL Week 8	OL Week 16	OL Week 24	OL Week 48	OL Week 72	OL Week 96
Data available	120	113	111	112	105	96	100	104
Data missing	0	7	9	8	15	24	20	16
Reason for missing								
Study discontinuation	0	0	0	0	1	2	4	9
Assessment done but not meeting criteria [a]	0	5	7	5	10	14	13	5
COVID-19 pandemic [b]	0	0	0	1	1	5	0	1
Other or unknown	0	2	2	2	3	3	3	1
Missing baseline [c]	n/a	0	0	0	0	0	0	0

- Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study.
- [a]: For analysis purposes, LCI data from visits with only one or no accepted replicate assessments were considered missing.
- [b]: missing due to COVID-19 pandemic is defined as (1) assessment not done and "Visit conduct was impacted by COVID-19" was recorded in the clinical data base or (2) "Visit was not conducted (in any format) due to COVID-19" was recorded in clinical data base.
- [c]: the post-baseline value is available but change from baseline is missing due to missing baseline. Only applicable to post baseline visits.

- Among the 41 (34.2%) subjects missing ppFEV1, reasons for missing data were assessment done but not meeting 2005 American Thoracic Society/European Respiratory Society criteria (n = 31) and study discontinuation (n = 10) (Table 30).

Table 30 Summary of Data Availability for Absolute Change from Baseline in ppFEV1 at Each Visit up to OL Week 96 OL Full Analysis Set

	Parent Study Baseline	OL Week 4	OL Week 8	OL Week 16	OL Week 24	OL Week 36	OL Week 48	OL Week 60	OL Week 72	OL Week 84	OL Week 96
Data available	120	94	88	95	94	86	70	83	72	78	79
Data missing	0	26	32	25	26	34	50	37	48	42	41
Reason for missing											
Study discontinuation	0	0	0	0	1	1	2	3	5	9	10
Assessment done but not meeting criteria [a]	0	26	32	23	21	30	40	31	40	30	31
COVID-19 pandemic [b]	0	0	0	1	2	1	5	0	0	1	0
Other or unknown	0	0	0	1	2	2	3	3	3	2	0
Missing baseline [c]	n/a	0	0	0	0	0	0	0	0	0	0

- Parent study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) before the first dose of study drug in the Treatment Period of the parent study.
- [a]: pulmonary functions test not meeting ATS criteria.
- [b]: missing due to COVID-19 pandemic is defined as (1) assessment not done and "Visit conduct was impacted by COVID-19" was recorded in the clinical data base or (2) "Visit was not conducted (in any format) due to COVID-19" was recorded in clinical data base.
- [c]: the post-baseline value is available but change from baseline is missing due to missing baseline. Only applicable to post baseline visits.

Missing data patterns at other visits are similar. Because assessments of multiple-breath washout, SwCl, or spirometry criteria were independent of the efficacy data, the missing-at-random assumption is reasonable. The MMRM analyses are appropriate under the missing-at-random assumption and are unbiased for the intended targets of estimation, which are the mean changes from baseline through Week 96 in the Study 119 population (as defined by the inclusion and exclusion criteria) for the ELX/TEZ/IVA and placebo groups, as randomized in parent Study 116.

Assessment of the response of the applicant

Patterns in the ad hoc tables show that the number of missings per category are fluctuating, which could be compatible with missing at random, depending on reason.

For the week 96 visit, only the reason “commercial drug availability” and “COVID-19” for missing data could be indicative of non-informative missingness. However, it cannot be fully assumed that assessment of multiple-breath washout, or spirometry are non-informative because it is not known whether this for pure technical reasons or the clinical condition of the subject. Furthermore ‘study discontinuations’ and ‘withdrawal of consent not for AE’ or ‘other or unknown’ could also still be informative of an inferior outcome. Therefore, (almost) all missing data could be informative. However, it is not uncommon that missing data are higher in a long-term safety study, while it was also during the COVID period. Taking into account the actual results that are generally consistent with the pivotal studies of Kaftrio and the pattern of the missingness, it seems that the high number of (potentially informative) missing data did not impact the reliability of the results. Therefore, considering the objective of the study, this not further pursued.

Conclusion

Issue not further pursued.

***Question* 6**

Related AEs are presented in an inconvenient table. The MAH is requested for a table containing related AE Adverse Events by Preferred Term OL Safety Set with cut-off of ≥5%.

Summary of the applicant's response

The requested table is provided below in Table 30.

Table 30 Related AEs Occurring in At Least 5% of Subjects by PT (OL Safety Set)

Preferred Term	Any ELX/TEZ/IVA N = 120 n (%)
Subjects with any related AEs	56 (46.7)
Alanine aminotransferase increased	7 (5.8)
Abdominal pain	6 (5.0)

Source: Study 119 aCSR/Table 14.3.2.1

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

Notes: AEs were coded using MedDRA version 25.1. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted.

Assessment of the response of the applicant

The applicant provided the requested table. Alanine aminotransferase increased and abdominal pain were the only related AEs with cut-off of ≥5%. Alanine aminotransferase increased and abdominal pain are common manifestations of CF disease, but occur also during the treatment with Kaftrio. No further action is required.

Conclusion

Issue resolved

***Question* 7**

In order to complete the evaluation of risk regarding hepatic events, the applicant is requested to discuss all reported hepatic AEs instead of solely the elevated transaminase events.

Summary of the applicant's response

Table 31 provides a summary of all hepatic AEs observed in Study 119.

Table 31 Summary of hepatic AEs by PT (OL Safety Set)

Preferred Term	Any ELX/TEZ/IVA N = 120 n (%)
Alanine aminotransferase increased	11 (9.2)
Aspartate aminotransferase increased	6 (5.0)
Hepatic cirrhosis	3 (2.5)
Hepatic steatosis	1 (0.8)
Hyperbilirubinaemia	1 (0.8)
Nodular regenerative hyperplasia	1 (0.8)
Portal hypertension	1 (0.8)

Source: Study 119 aCSR/Table 14.3.1.2

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

Notes: AEs were coded using MedDRA version 25.1. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

Because elevated transaminase events were considered AEs of special interest in Study 119, they were specifically discussed in the aCSR. However, as requested, Vertex has included its review of all reported AEs under the System Organ Class "hepatobiliary disorders" below.

A total of 6 subjects had 7 events of hepatobiliary disorders, 2 of whom also had elevated transaminase events. The reported events occurred from 1.5 months to 1 year after ELX/TEZ/IVA initiation in parent Study 116 or open-label extension (OLE) Study 119. None of the events led to change in study drug dosing. The majority of the reported events were considered unlikely or not related to study drug by the investigator. Of the 6 subjects, 5 had a history of CF hepatic disease or previous elevations of transaminase and/or bilirubin levels. Of the 2 events considered possibly related to ELX/TEZ/IVA treatment by the investigator, both were ongoing at the end of the study participation without change to study drug dosing.

Overall, Vertex assesses that these events are consistent with background CF-related hepatic disease and the established safety profile of ELX/TEZ/IVA. Therefore, there are no new safety concerns based on the reported hepatic AEs.

Overall, Vertex assesses that these hepatobiliary events seen in Study 119 are consistent with background CF-related hepatic disease, which is a well-established comorbidity in people with CF, as well as the established safety profile of ELX/TEZ/IVA. Therefore, there are no new safety concerns based on the reported hepatic AEs.

REFERENCES

1 Nodular Regenerative Hyperplasia. In: editors. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

Assessment of the response of the applicant

In addition to the events of elevated transaminases, 6 subjects had 7 events of hepatobiliary disorders.

The subjects' summaries were presented. Most of the subjects had already a medical history of CF hepatic disease or liver function test fluctuations. Only 1 subject did not had a history of CF hepatic disease, but the new developed hepatic steatosis was considered unlikely related to study drug by the investigator. However, it is noted that clinically significant liver cirrhosis (with or without portal hypertension) was an exclusion criterion (see question 3). It seems that some of the above patients had a pre-existing liver cirrhosis, and the clinically relvance can be questioned.

Nevertheless, the assessment of the applicant of the cases is accepted. As a warning to be cautious with use in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) is already included in the SmPC, a change of the SmPC is not warranted as the information of these new cases has not lead to new information.

Conclusion

Issue resolved.