25 May 2023
EMA/266901/2023
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/P46/010

Note

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

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Table of contents

1. Introduction

On January 13th 2023, the MAH submitted a completed paediatric study for Kaftrio, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Kaftrio is currently indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Kaftrio obtained initially a marketing authorization in patients aged 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for *F508del* in the CFTR gene with a minimal function (MF) mutation in 2020. In 2021, the indication was extended to patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Recently, the indication was extended to children with CF aged 6 years through 11.

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

Within this procedure, the MAH submitted final study results of Study VX19-445-117, a Phase 3b, open-label study in CF subjects 12 years of age and older, heterozygous for *F508del* and a minimal function mutation (F/MF genotypes), with abnormal glucose tolerance. The MAH stated that Study VX19-445-117 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study VX19-445-117, the study drug was administered orally as 2 ELX 100 mg/TEZ 50 mg/IVA 75 mg tablets in the morning and 1 tablet of IVA 150 mg in the evening. This pharmaceutical formulation and posology are authorized for patients aged 6 and older, weighing 30 kg or more and thereby also for the study population aged 12 years and older.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study VX19-445-117 (Study 117) was a Phase 3b, open-label study in CF subjects 12 years of age and older, heterozygous for *F508del* and a minimal function mutation (F/MF genotypes), with abnormal glucose tolerance.

2.3.2. Clinical study

Study VX19-445-117 (Study 117)

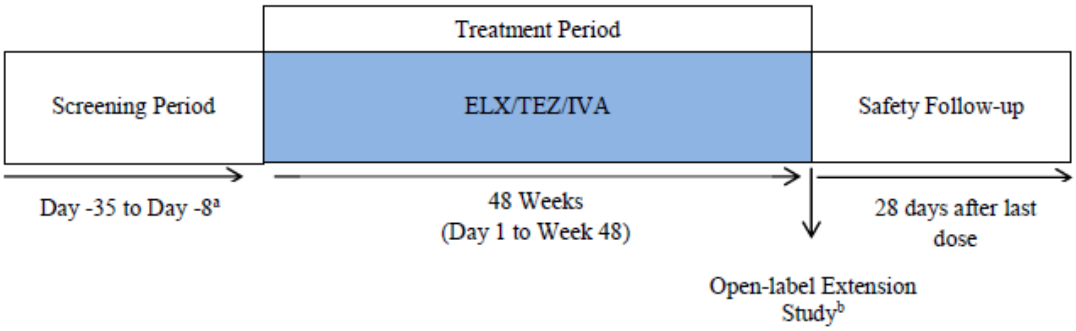
Description

Study VX19-445-117 (Study 117) was a Phase 3b, open-label study in CF subjects 12 years of age and older, heterozygous for F508del and a minimal function mutation (F/MF genotypes), with abnormal glucose tolerance.

The study design is shown in

Figure 1.

Figure 1. Study 117 Study design



ELX: elexacaftor; CFRD: CF-related diabetes; CGM: continuous glucose monitoring; IVA: ivacaftor; TEZ: tezacaftor

[a] On Day -7, a CGM sensor was inserted subcutaneously to assess baseline blood glucose levels for 7 days prior to the first dose of study drug in subjects with CFRD.

[b] Subjects who completed the visits in the Treatment Period, regardless of whether they were on a treatment interruption, were offered the opportunity to enroll in an open-label extension safety study evaluating ELX/TEZ/IVA. The Safety Follow-up Visit was not required for subjects who completed the Week 48 Visit and enrolled in an open-label extension study, or who transitioned to a commercially available CFTR modulator regimen, within 28 days after the last dose of study drug.

Methods

Study participants

The study included patients aged 12 years and older with F/MF *CFTR* genotype, ppFEV1 value ≥30% and stable CF disease. Eligible patients also had to have abnormal glucose tolerance as determined by an OGTT at Screening (Table 1).

Table 1. Key eligibility criteria Study 117

Inclusion Criteria	Exclusion Criteria

• F/MF *CFTR* genotypes
• 12 years of age or older
• FEV_1 value ≥30% of predicted mean for age, sex, and height (equations of the GLI)[1] at the Screening Visit (spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[2] for acceptability and repeatability)
• Stable CF disease as judged by the investigator
• Abnormal glucose tolerance as determined by an OGTT, classified as either:
  ○ **IGT:** defined as 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL (≥7.77 to <11.10 mmol/L), or
  ○ **CFRD:** defined as either fasting hyperglycemia (blood glucose level ≥126 mg/dL [≥7.00 mmol/L] after an 8-hour fast) or 2-hour post-OGTT blood glucose level ≥200 mg/dL (≥11.10 mmol/L)
	• History of any illness or clinical condition that could confound the results of the study
	• Type 1 or Type 2 diabetes
	• Duration of CFRD ≥5 years
	• Any protocol-defined laboratory values indicative of abnormal liver function or abnormal renal function
	• Any acute upper or lower respiratory infection, PEx, or changes in therapy for pulmonary disease within 28 days before first dose of study drug (Day 1)
	• Colonization with organisms associated with a more rapid decline in pulmonary status
	• An acute illness not related to CF within 14 days before the first dose of study drug (Day 1)
	• Use of restricted medication (including antidiabetic medication other than insulin, which must be at a dose no greater than 0.3 units/kg/day) within specified duration before the first dose of study drug
	• BMI ≥30 kg/m^2 at the Screening Visit
	• Pregnant or breast-feeding females

Sources: Study 117 Protocol/Sections 8.1 and 8.2
BMI: body mass index; CF: cystic fibrosis; CFRD: cystic fibrosis-related diabetes; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; FEV_1: forced expiratory volume in 1 second; F/MF: heterozygous for *F508del* and a minimal function mutation; GLI: Global Lung Function Initiative; IGT: impaired glucose tolerance; OGTT: oral glucose tolerance test; PEx: pulmonary exacerbation

Treatments

Study drug tablets were administered orally as ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Patients received 2 ELX 100 mg/TEZ 50 mg/IVA 75 mg tablets in the morning and 1 tablet of IVA 150 mg in the evening. Study drug was administered within approximately 30 minutes of consumption of a fat-containing meal or snack.

During the Treatment Period, patients were to be administered ELX/TEZ/IVA for approximately 48 weeks.

Objective(s)

The primary objective was to evaluate the effect of ELX/TEZ/IVA on glucose tolerance in CF subjects with impaired glucose tolerance (IGT) or CF-related diabetes (CFRD).

The secondary objective was to evaluate safety and tolerability of ELX/TEZ/IVA.

Outcomes/endpoints

Primary endpoint

The change from baseline in 2-hour blood glucose levels following an oral glucose tolerance test (OGTT) to the average of Week 36 and Week 48.

Secondary endpoints

- Proportion of subjects with improvement in dysglycaemia categorization (CFRD, IGT, normal glucose tolerance [NGT]) at Week 48.
- Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry.

Other endpoints

- Change from baseline in sweat chloride (SwCl) through Week 48
- Absolute change in body mass index (BMI) from baseline at Week 48
- Absolute change in body weight from baseline at Week 48
- Change from baseline in hemoglobin A1c (HbA1c) and fructosamine at Week 48
- Change from baseline in insulin use (dose) at Week 48 in subjects using insulin
- Change from baseline in post-OGTT diabetes-related biomarkers (including insulin, C-peptide, glucagon, calculated indices of insulin secretion [insulinogenic index], and insulin resistance [HOMA-IR]) at Week 48
- Change from baseline in biomarkers of inflammation (including C-reactive protein [CRP]) at Week 48
- Change from baseline in biomarkers of pancreatic function (including fecal elastase-1 [FE-1] and serum immunoreactive trypsinogen [IRT]) at Week 48
- Change from baseline in post-OGTT incretin levels (including glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) at Week 48
- Change from baseline in percent of time spent in target blood glucose range of ≥70 to <140 mg/dL (≥3.89 to <7.77 mmol/L) as measured by 7-day continuous glucose monitoring (CGM) in subjects with CFRD at Week 48
- Change from baseline in selected continuous glucose monitoring (CGM) parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time spent ≥200 mg/dL [≥11.10 mmol/L], and mean amplitude of glycemic excursion* [MAGE]) in subjects with CFRD at Week 48

*Note: definition corrected for MAGE (originally defined as maximum amplitude of glucose excursions in the study protocol).

Sample size

Assuming a within group standard deviation (SD) of 45 mg/dL and a 10% dropout rate at Week 48, a sample size of 60 subjects was considered to have more than 95% power to detect a mean decrease from baseline of -30 mg/dL in 2-hour blood glucose levels post-OGTT to the average of Week 36 and Week 48, based on a 2-sided, 1-sample t-test at a significance level of 0.05.

Therefore, approximately 60 subjects (F/MF genotypes) were planned to be enrolled, of whom approximately 30 subjects with IGT, and 30 subjects with CFRD.

Randomisation and blinding (masking)

Not applicable, as this is an open-label single arm trial.

Statistical Methods

Analysis sets

All Subjects Set - all subjects who were enrolled. This analysis set was used for all individual subject data listings and disposition summary tables, unless otherwise specified.

Full Analysis Set (FAS) - all enrolled subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS was used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy endpoints, unless otherwise specified.

Safety Set - all subjects who have received at least 1 dose of study drug. The Safety Set was used for all safety analyses.

Efficacy analyses

The primary null hypothesis to be tested was that the mean change from baseline in 2-hour blood glucose levels following OGTT to the average of Week 36 and Week 48 is equal to zero.

OGTT results were considered valid only when the subject was fasting for at least 8 hours. Any non-fasting OGTT results were disregarded and data for that assessment was considered missing.

The primary analysis was performed using a mixed-effects model for repeated measures (MMRM) with the change from baseline in 2-hour post-OGTT blood glucose levels at each post-baseline visit as the dependent variable. The primary result obtained from the model was the estimated change from baseline to the average of Week 36 and Week 48. Data obtained from Week 24, Week 36, and Week 48 visits were included in the model. The least square (LS) mean estimate along with the corresponding 2-sided 95% CI and probability (*P*) value were provided. The LS mean change from baseline at each post-baseline visit with 95% CI, obtained from the model, were also provided. Furthermore, the LS mean change from baseline (with SE) at each post-baseline visit, obtained from the model, was plotted.

In addition, the post-baseline raw values and the change from baseline at each post-baseline visit up to Week 48 were summarized descriptively (n, mean, SD, median, minimum, and maximum).

For the secondary endpoint, improvement in dysglycaemia categorization, abnormal or normal glucose tolerance (NGT) as determined by an OGTT, were classified as either:

- CFRD: 2-hour post-OGTT blood glucose level ≥200 mg/dL (≥11.10 mmol/L) or fasting hyperglycemia (blood glucose level ≥126 mg/dL [≥7.00 mmol/L] after an 8-hour fast)
- IGT: 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL (≥7.77 to <11.10 mmol/L) and fasting blood glucose level <126 mg/dL (<7.00 mmol/L)
- NGT: 2-hour post-OGTT blood glucose level <140 mg/dL (<7.77 mmol/L) and fasting blood glucose level <126 mg/dL (<7.00 mmol/L)

Improvement in dysglycaemia categorization: response at Week 48 compared to baseline (i.e., CFRD at baseline to IGT or NGT at Week 48, or IGT at baseline to NGT at Week 48 OGTT).

The number and proportion of subjects with and without response at Week 48, defined as improvement from baseline dysglycaemia categorization (i.e., CFRD at baseline to IGT or NGT based on Week 48 OGTT measurement, and IGT at baseline to NGT based on Week 48 OGTT measurement), were presented for patients with abnormal glucose (CFRD or IGT) at baseline. The exact, 2-sided 95% Clopper-Pearson CI of the proportion of subjects with improvement was also presented. In addition, the number and proportion of subjects in each dysglycaemia category at baseline and each post-baseline visit were presented.

Multiplicity control – No multiplicity adjustment was performed.

Interim analysis - No interim analysis was planned.

Handling of missing values/censoring/discontinuations - Incomplete/missing data were not planned to be imputed, unless specified otherwise.

Results

Participant flow

A total of 69 patients enrolled and received at least 1 dose of study drug, and 66 (95.7%) patients completed study drug treatment (Table 2). Three (4.3%) patients discontinued treatment: 2 due to commercial drug availability and 1 due to physician decision.

Table 2. Subject Disposition (All Subjects Set)

Disposition/Reason	ELX/TEZ/IVA n (%)
All Subjects Set	69
Full Analysis Set	69
Safety Set	69
Completed treatment	66 (95.7)
Discontinued treatment	3 (4.3)
Reason for discontinuation of treatment	
Commercial drug is available for subject	2 (2.9)
Physician decision	1 (1.4)
Completed study	66 (95.7)
Discontinued study	3 (4.3)
Reason for discontinuation from study	
Withdrawal of consent (not due to AE)	2 (2.9)
Physician decision	1 (1.4)
Rollover to the open-label study	
Yes	31 (44.9)
No	38 (55.1)

Source: Table 14.1.1
AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor
Notes: All Subjects Set: all subjects who were enrolled. Full Analysis Set: all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. Safety Set: all subjects who received at least 1 dose of study drug.

Recruitment

Study initiation: 15 January 2021 (date first eligible subject signed the informed consent form)

Study completion: 14 July 2022 (date last subject completed the last visit)

The study was conducted at 38 sites in Australia and the EU.

Conduct of study

Protocol amendments

The original study protocol dated 24 August 2020 was amended twice (Sept 2020 and Apr 2021). Changes mostly pertained clarifications and updates in exploratory endpoint definitions or measurements. In addition, the definition of IGT and CFRD was updated to eliminate a gap in glucose values in previous protocol versions. There were no changes in conduct to the statistical analysis plan.

Protocol deviations

Two patients had important protocol deviations: one patient had study drug compliance of 71% and the other patient did not fast prior to the OGTT at Week 48.

Baseline data

The included study population had a median age of 22.7 years (min, max 12.7, 51.5), 27.5% (n=19) of patients were <18 years of age and 55.1% was male (Table 3). The majority of patients (69.6%) were White, and 11.6% were Hispanic or Latino. At screening, 40 (58%) subjects were classified as having CFRD and 29 (42%) subjects were classified as having IGT based on the OGTT (Table 4). At baseline, the mean 2-hour post-OGTT blood glucose level was 217.6 mg/dL, and 20 (29%) subjects were receiving insulin; subjects were counseled on the safe withholding of insulins prior to each OGTT. The most common concomitant medications were those typically used for the management of CF; anti-diabetic medications, except for exogenous (subcutaneously injected) insulins, were prohibited per the protocol.

Table 3. Demographics (FAS)

Demographic	ELX/TEZ/IVA N = 69
Sex, n (%)	
Male	38 (55.1)
Female	31 (44.9)
Childbearing potential, n (%)	
Yes	31 (100.0)
No	0
Age at baseline (years)	
N	69
Mean (SD)	25.1 (9.5)
Median	22.7
Min, max	12.7, 51.5
Age category at baseline, n (%)	
<18 years	19 (27.5)
≥18 years	50 (72.5)
Race, n (%)	
White	48 (69.6)
Black or African American	0
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other	1 (1.4)
Not collected per local regulations	20 (29.0)
Ethnicity, n (%)	
Hispanic or Latino	8 (11.6)
Not Hispanic or Latino	41 (59.4)
Not collected per local regulations	20 (29.0)
Country, n (%)	
Australia	11 (15.9)
Belgium	7 (10.1)
Czech Republic	3 (4.3)
France	13 (18.8)
Italy	12 (17.4)
Netherlands	9 (13.0)
Spain	14 (20.3)

Source: Table 14.1.3
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. If a subject was reported to have multiple races, then the subject was counted for each race reported.

Table 4. Baseline characteristics (FAS)

Characteristic	ELX/TEZ/IVA N = 69
Weight (kg)	
n	69
Mean (SD)	56.2 (9.5)
Median	56.4
Min, max	36.7, 82.9
Height (cm)	
n	69
Mean (SD)	165.0 (8.2)
Median	165.0
Min, max	148.8, 181.5
BMI (kg/m^2)	
n	69
Mean (SD)	20.54 (2.60)
Median	20.62
Min, max	15.88, 26.74
$ppFEV_1$ category at baseline, n (%)	
<30	1 (1.4)
≥30 to <40	7 (10.1)
≥40 to <70	30 (43.5)
≥70 to ≤90	16 (23.2)
>90	15 (21.7)
$ppFEV_1$ at baseline	
n	69
Mean (SD)	69.5 (22.2)
Median	65.6
Min, max	26.2, 115.8
Sweat chloride (mmol/L) at baseline	
n	69
Mean (SD)	95.5 (12.1)
Median	99.0
Min, max	56.5, 116.5
2-hour post-OGTT blood glucose (mg/dL) levels at baseline	
n	69
Mean (SD)	217.6 (73.1)
Median	206.1
Min, max	107.1, 456.2
Dysglycemia categorization at screening, n (%)	
IGT	29 (42.0)
CFRD	40 (58.0)
Insulin use at baseline, n (%)	
Yes	20 (29.0)
No	49 (71.0)

Table continued

Characteristic	ELX/TEZ/IVA N = 69
Prior use of dornase alfa,[a] n (%)	
Yes	49 (71.0)
No	20 (29.0)
Prior use of azithromycin,[a] n (%)	
Yes	35 (50.7)
No	34 (49.3)
Prior use of inhaled antibiotic,[a] n (%)	
Yes	28 (40.6)
No	41 (59.4)
Prior use of any bronchodilator,[a] n (%)	
Yes	59 (85.5)
No	10 (14.5)
Prior use of any inhaled bronchodilator,[a] n (%)	
Yes	57 (82.6)
No	12 (17.4)
Prior use of any inhaled hypertonic saline,[a] n (%)	
Yes	37 (53.6)
No	32 (46.4)
Prior use of any inhaled corticosteroids,[a] n (%)	
Yes	42 (60.9)
No	27 (39.1)

Source: Table 14.1.4

BMI: body mass index; CFRD: cystic fibrosis-related diabetes; ELX: elexacaftor; FAS: Full Analysis Set; IGT: impaired glucose tolerance; IVA: ivacaftor; n: size of subsample; N: total sample size; OGTT: oral glucose tolerance test; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. Baseline 2-hour post-OGTT blood glucose level is defined as the average of valid pre-dose measurements at Screening and Day 1. OGTT results are considered valid only when the subject was fasting for at least 8 hours.

[a] Includes medications administered during the 56 days before the first dose of study drug.

Number analysed

The final number of patients in each analysis set is shown in Table 5.

Table 5. Patient disposition

Analysis Set	ELX/TEZ/IVA n
All Subjects Set	69
Full Analysis Set	69
Safety Set	69

Source: Table 14.1.1

Notes: All Subjects Set: all subjects who were enrolled. Full Analysis Set: all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. Safety Set: all subjects who received at least 1 dose of study drug.

Efficacy results

Primary endpoint - *The change from baseline in 2-hour blood glucose levels following an oral glucose tolerance test (OGTT) to the average of Week 36 and Week 48.*

Treatment with ELX/TEZ/IVA resulted in a statistically significant mean within-group change of -35.0 mg/dL (95% CI: -49.2, -20.7; P<0.0001) in the 2-hour post-OGTT blood glucose levels from baseline to the average of Weeks 36 and 48 (Table 6).

Table 6. MMRM analysis of absolute change from baseline in 2-hour post-OGTT blood glucose level at average of Week 36 and Week 48 (FAS)

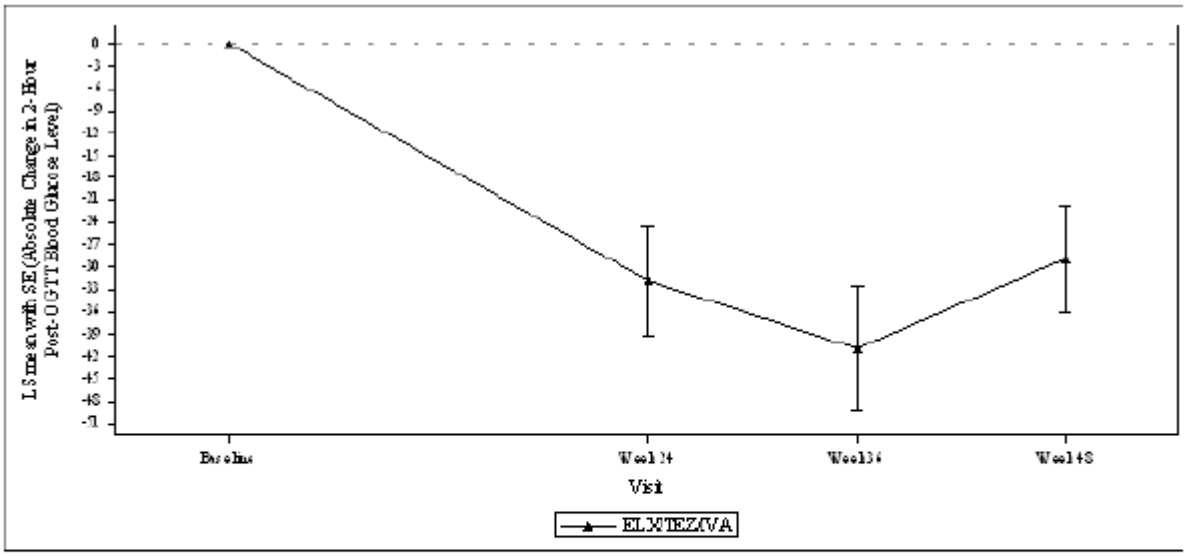
	ELX/TEZ/IVA N = 69
Baseline	
n	69
Mean (SD)	217.6 (73.1)
Absolute change at average of Week 36 and Week 48	
n	66
LS mean (SE)	-35.0 (7.1)
95% CI of LS mean	(-49.2, -20.7)
P value	<0.0001

Source: Table 14.2.1.2

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; OGTT: oral glucose tolerance test; TEZ: tezacaftor

Notes: Baseline 2-hour post-OGTT blood glucose level was defined as the average of valid pre-dose measurements at Screening and Day 1. OGTT results were considered valid only when the subject was fasting for at least 8 hours. MMRM included data from all available visits up to Week 48, with visit as fixed effect and baseline 2-hour post-OGTT blood glucose level as covariate. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Figure 2. MMRM analysis of absolute change from baseline in 2-hour post-OGTT blood glucose level at each visit up to week 48 (FAS)



Source: Figure 14.2.1

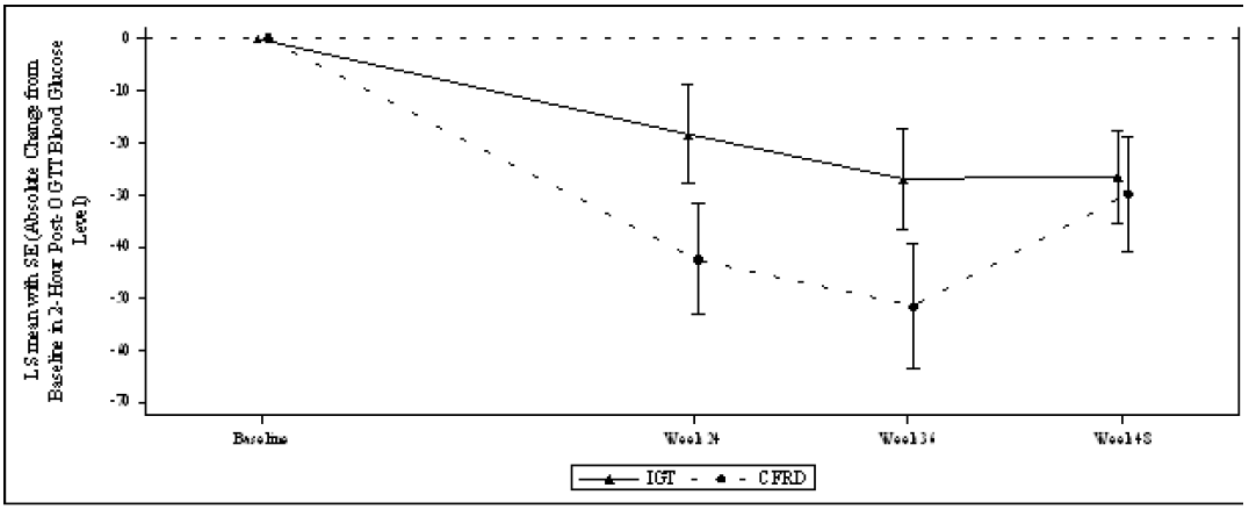
ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OGTT: oral glucose tolerance test; TEZ: tezacaftor

Notes: Baseline 2-hour post-OGTT blood glucose level was defined as the average of valid pre-dose measurements at Screening and Day 1. OGTT results were considered valid only when the subject was fasting for at least 8 hours. MMRM included data from all available visits up to Week 48, with visit as fixed effect and baseline 2-hour post-OGTT blood glucose level as covariate. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Improvements in mean 2-hour post-OGTT blood glucose levels were seen in both the IGT and CFRD subject subgroups (Figure 3):

- Of the subjects in the IGT category at screening, ELX/TEZ/IVA resulted in a mean within-group change of -26.7 mg/dL (95% CI: -44.1, -9.4) in the 2-hour post-OGTT blood glucose levels from baseline to the average of Weeks 36 and 48.
- Of the subjects in the CFRD category at screening, ELX/TEZ/IVA resulted in a mean within-group change of -40.7 mg/dL (95% CI: -62.3, -19.1) in the 2-hour post-OGTT blood glucose levels from baseline to the average of Weeks 36 and 48.

Figure 3. MMRM analysis of absolute change from baseline in 2-hour post-OGTT blood glucose level at each visit up to week 48 by dysglycemia categorization at screening (FAS)



Source: Ad hoc Figure 14.2.1.3

CFRD: cystic fibrosis-related diabetes; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OGTT: oral glucose tolerance test; TEZ: tezacaftor

Notes: Baseline 2-hour post-OGTT blood glucose level was defined as the average of valid pre-dose measurements at Screening and Day 1. OGTT results were considered valid only when the subject was fasting for at least 8 hours. CFRD: 2-hour post-OGTT blood glucose level ≥200 mg/dL (≥11.10 mmol/L) or fasting blood glucose level ≥126 mg/dL (≥7.00 mmol/L); IGT: 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL (≥7.77 to <11.10 mmol/L) and fasting blood glucose level <126 mg/dL (<7.00 mmol/L). MMRM included data from all available visits up to Week 48, with visit as fixed effect and baseline 2-hour post-OGTT blood glucose level as covariate. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Secondary endpoint - *Proportion of subjects with improvement in dysglycaemia categorization (CFRD, IGT, normal glucose tolerance [NGT]) at Week 48.*

Treatment with ELX/TEZ/IVA resulted in an improvement in dysglyacemia category from baseline to Week 48 in 20 (37.7%) subjects (95% CI: 24.8%, 52.1%; Table 7).

Table 7. Improvement in dysglycaemia categorization in patients with abnormal glucose tolerance at baseline (FAS)

Visit	ELX/TEZ/IVA N1 = 60 n (%)
Baseline	
N1	60
IGT	28 (46.7)
CFRD	32 (53.3)
Week 48	
n1	53
NGT	14 (26.4)
IGT	17 (32.1)
CFRD	22 (41.5)
Improvement in dysglycemia categorization at Week 48	
n1	53
Subjects without improvement	33 (62.3)
Subjects with improvement	20 (37.7)
Exact 95% CI for percentage of subjects with improvement (%)	(24.8, 52.1)

Source: Table 14.2.2.1

CFRD: cystic fibrosis-related diabetes; ELX: elexacaftor; FAS: Full Analysis Set; IGT: impaired glucose tolerance; IVA: ivacaftor; n: number of subjects with the specified dysglycemia categorization; N1: number of subjects with abnormal glucose at baseline; n1: number of subjects with non-missing dysglycemia categorization at Week 48, among subjects with abnormal glucose tolerance and baseline; NGT: normal glucose tolerance; OGTT: oral glucose tolerance test; TEZ: tezacaftor

Notes: Baseline dysglycemia category was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. OGTT results were considered valid only when the subject was fasting for at least 8 hours. CFRD: 2-hour post-OGTT blood glucose level ≥200 mg/dL (≥11.10 mmol/L) or fasting blood glucose level ≥126 mg/dL (≥7.00 mmol/L); IGT: 2-hour post-OGTT blood glucose level ≥140 to <200 mg/dL (≥7.77 to <11.10 mmol/L) and fasting blood glucose level <126 mg/dL (<7.00 mmol/L); NGT: 2-hour post-OGTT blood glucose level <140 mg/dL (<7.77 mmol/L) and fasting blood glucose level <126 mg/dL (<7.00 mmol/L). Improvement: CFRD at baseline to IGT/NGT at Week 48 or IGT at baseline to NGT at Week 48.

- Twenty-two (35.5%) subjects achieved NGT at Week 48 (95% CI: 23.7%, 48.7%) compared to 9 (13.0%) subjects at baseline.
- Improvements in dysglycaemia categorization were seen in both the IGT and CFRD subject subgroups (Figure 3):
    - Of the subjects in the IGT category at baseline, 10 (38.5%) had improvement in dysglycaemia category at Week 48.
    - Of the subjects in the CFRD category at baseline, 10 (37%) had improvement in dysglycaemia category at Week 48.

Exploratory endpoints

- The mean change from baseline in sweat chloride (SwCl) through Week 48 was -48.7 mmol/L (SD: 16.4), indicating an improvement (reduction) in SwCl with ELX/TEZ/IVA treatment.
- The mean absolute change in body mass index (BMI) from baseline at Week 48 was 1.57 (SD:1.32) kg/m^2.

- The mean absolute change in body weight from baseline at Week 48 was 4.8 (SD:3.6) kg.
- The change from baseline in selected CGM parameters (including but not limited to percent of time spent between ≥140 and <200 mg/dL [≥7.77 and <11.10 mmol/L], percent of time spent ≥200 mg/dL [≥11.10 mmol/L]) at Week 48 as measured by 7-day CGM in patients with CFRD is presented in Table 8.

Table 8. Change from baseline in CGM parameters at Week 48 in patients with CFRD at screening (FAS)

CGM Endpoints	ELX/TEZ/IVA N = 40			
	Baseline		Change from Baseline at Week 48	
	n	Mean (SD)	n	Mean (SD)
Percent of time spent:				
≥70 to <140 mg/dL (target range)	38	59.3 (18.6)	27	1.6 (18.5)
≥140 to <200 mg/dL	38	28.9 (12.0)	27	-2.4 (13.3)
≥200 mg/dL	38	10.4 (10.2)	27	0.7 (15.8)

Sources: Tables 14.2.3.3.1, 14.2.3.3.2, and 14.2.3.3.3
CGM: continuous glucose monitoring; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. The daily continuous glucose monitoring assessment was considered valid when at least 202 valid values were obtained (at least 70% of 288 5-minute records). For each visit, the value was calculated by averaging the valid daily assessments, provided that there were at least 4 valid daily assessments.

Of note: outcomes for the CGM parameter 'mean amplitude of glycemic excursion* [MAGE] in subjects with CFRD at Week 48' as well as the other pre-defined exploratory endpoints have not been presented by the MAH.

Safety results

Safety was analysed in 69 patients of Study 117, who had received at least 1 dose of study drug in the treatment period (Safety Set).

Exposure

The median (min, max) exposure in the Safety Set was 48 weeks (32.0, 52.3; Table 9).

Table 9. Summary of exposure (safety set)

	ELX/TEZ/IVA N = 69
Total exposure (patient weeks)	3284.3
Exposure duration (weeks)	
n	69
Mean (SD)	47.6 (3.0)
Median	48.0
Min, max	32.0, 52.3
Exposure duration by interval, n (%)	
>0 to ≤1 week	0
>1 to ≤4 weeks	0
>4 to ≤12 weeks	0
>12 to ≤24 weeks	0
>24 to ≤36 weeks	3 (4.3)
>36 to ≤48 weeks	35 (50.7)
>48 weeks	31 (44.9)

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

Adverse events

Almost all patients (97.1%) experienced at least 1 adverse event (AE; Table 10). Most AEs were mild or moderate in severity, and 10 (14.5%) patients had severe AEs. Six (8.7%) subjects had serious adverse events (SAEs), none of which were considered to be related to study drug. There were no life-threatening AEs or deaths.

Table 10. Overview of AEs (Safety Set)

Category	ELX/TEZ/IVA N = 69 n (%)
Number of AEs (total)	516
Subjects with any AEs	67 (97.1)
Subjects with AEs by strongest relationship	
Not related	23 (33.3)
Unlikely related	4 (5.8)
Possibly related	30 (43.5)
Related	10 (14.5)
Subjects with AEs by maximum severity	
Grade 1/Mild	26 (37.7)
Grade 2/Moderate	31 (44.9)
Grade 3/Severe	10 (14.5)
Grade 4/Life-threatening	0
Grade 5/Death	0
Subjects with AEs leading to study drug discontinuation	0
Subjects with AEs leading to study drug interruption	5 (7.2)
Subjects with Grade 3/4/5 AEs	10 (14.5)
Subjects with related AEs[a]	40 (58.0)
Subjects with SAEs	6 (8.7)
Subjects with related SAEs[a]	0
Subjects with AEs leading to death	0

Source: Table 14.3.1.1

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

Notes: AEs were coded using MedDRA version 25.0. A subject with multiple events within a category is counted only once with the maximum severity in that category according to the order, where the order of decreasing severity is: 1. Death, 2. Life-threatening, 3. Severe, 4. Moderate, 5. Mild, and 6. Missing. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category is counted only once in that category. An AE with relationship missing is counted as related.

[a] When summarizing number of subjects with related AEs and SAEs, AEs with relationship of related, possibly related, and missing were counted.

Common adverse events

AEs that occurred in ≥10% of patients are shown in Table 11. The most common adverse events were COVID-19 (31.9%), headache (23.2%), pyrexia (23.2%), and nasopharyngitis (21.7%).

Table 11. AEs occurring in at least 10% of patients by PT (Safety Set)

Preferred Term	ELX/TEZ/IVA N = 69 n (%)
Subjects with any AEs	67 (97.1)
COVID-19	22 (31.9)
Headache	16 (23.2)
Pyrexia	16 (23.2)
Nasopharyngitis	15 (21.7)
Diarrhea	13 (18.8)
Sputum increased	12 (17.4)
Cough	11 (15.9)
Infective pulmonary exacerbation of CF	10 (14.5)
Abdominal pain	9 (13.0)
Abdominal pain upper	8 (11.6)
Oropharyngeal pain	8 (11.6)
Blood bilirubin increased	7 (10.1)
Influenza	7 (10.1)
Rash	7 (10.1)
Rhinitis	7 (10.1)
Vomiting	7 (10.1)

Source: Table 14.3.1.3

AE: adverse event; COVID-19: coronavirus disease; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: preferred term; TEZ: tezacaftor

Notes: AEs were coded using MedDRA version 25.0. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

Severity of adverse events

Most patients had AEs that were mild or moderate in severity. In total ten (14.5%) patients had severe AEs, which were all grade 3 events reported for one or two patients each.

Relationship of adverse events

Ten (14.5%) patients had AEs that were assessed by the investigator as related to study drug, and 30 (43.5%) patients had AEs that were assessed by the investigator as possibly related to study drug. AEs at least possibly related to study drug were most frequently reported for system organ class (SOC) investigations (21.7%), followed by skin- and subcutaneous tissue disorders (18.8%), gastrointestinal disorders and respiratory, thoracic and mediastinal disorders (17.4% each).

The most common (>5%) at least possibly related AEs were sputum increased (10.1%), cough (7.2%), blood bilirubin increased (8.7%), rash (7.2%), abdominal pain (7.2%), headache (5.8%), diarrhoea (5.8%), alanine aminotransferase increased (5.8%).

Deaths and other serious adverse events

There were no life-threatening AEs or deaths.

Six (8.7%) patients had SAEs, none of which were considered to be related to study drug. These SAEs were mostly reported within the SOC infections and infestations (3 patients, 4.3%), i.e.: infective pulmonary exacerbation of CF, influenza and sinusitis.

Study drug discontinuation

No patients had AEs that led to discontinuation of study drug. Five (7.2%) patients interrupted study drug due to AEs of rash (2.9%), urticaria (1.4%), increased alanine aminotransferase (2.9%),

increased aspartate aminotransferase (2.9%), increased blood creatinine phosphokinase (1.4%), abdominal pain (1.4%) and pyrexia (1.4%).

Adverse events of special interest

Elevated transaminase event

Seven (10.1%) patients had nonserious elevated transaminase events, most of which were assessed by the investigator as mild or moderate in severity. Two (2.9%) patients had elevated transaminase events that led to study drug interruption and no subjects had elevated transaminase events that led to discontinuation.

Rash events

Twelve (17.4%) patients had at least 1 rash event. Most patients had rash events that were mild or moderate in severity; none were serious. Three (4.3%) patients had rash events that led to treatment interruption, all of whom resumed study drug. There were no study drug discontinuations due to rash events.

By sex, 5 (16.1%) female patients and 7 (18.4%) male patients had rash events. Of the female patients with rash events, 3 (27.3%) patients had concomitant use of hormonal therapy, and 2 (10.0%) patients did not.

Clinical laboratory evaluation

Chemistry

Elevated transaminase events - are described above.

Creatinine kinase (CK) – The majority of subjects had CK levels ≤2.5 x upper limit of normal (ULN); 4 (5.8%) subjects had CK levels >5 × ULN. AEs of blood CK increased were reported in 5 (7.2%) of patients.

Other chemistry parameters - Six patients (8.7%) had AEs related to chemistry findings (excluding liver function tests and CK), all of these were mild or moderate in severity and none led to treatment interruption or discontinuation.

Hematology

There were no trends observed in hematology parameters. Three (4.3%) subjects had AEs related to hematology findings (anaemia/red blood cell count decreased and platelet count decreased).

Vital signs

There were no trends observed in the vital signs or ECG parameters. No patients had AEs related to vital signs values.

2.3.3. Discussion on clinical aspects

Design and conduct

With this article 46 procedure, the MAH presented final study results of Study VX19-445-117, a Phase 3b, open-label study in CF subjects 12 years of age and older, heterozygous for *F508del* and a minimal function mutation (F/MF genotypes), with abnormal glucose tolerance. Study VX19-445-117 is a standalone study. No changes to the current product information for Kaftrio have been proposed.

Study 117 was designed to evaluate the effect of ELX/TEZ/IVA on glucose tolerance in CF subjects with impaired glucose tolerance (IGT) or CF-related diabetes (CFRD). Due to the single arm trial design and

lack of discussion on the minimal important clinical difference in CF for the main clinical endpoints, interpretation of obtained results is hampered.

The investigated dose of ELX/TEZ/IVA is identical to the registered posology for the study population.

It is acceptable that results for some exploratory endpoints (i.e. change from baseline in: CGM parameter MAGE in patients with CFRD at Week 48, HbA1C, insulin use, post-OGTT diabetes-related biomarkers, biomarkers of inflammation, biomarkers of pancreatic function and post-OGTT incretin levels) have not been presented by the Applicant, as none of these endpoints are validated in CF-related diabetes and interpretation is limited.

Results

Efficacy

A total of 69 patients enrolled and received at least 1 dose of study drug, and 66 (95.7%) patients completed study drug treatment. The median age of the study population was 22.7 years, with 19 patients (27.5%) <18 years of age. At screening, 58% of patients was classified as having CFRD and 42% was classified as having IGT based on the OGTT. At baseline, 29% of patients was receiving insulin.

The primary endpoint was met with a statistically significant mean within-group change of -35.0 mg/dL (95% CI: -49.2, -20.7; P<0.0001) in the 2-hour post-OGTT blood glucose levels from baseline to the average of Weeks 36 and 48. Results in the subgroups of CFRD and IGT patients indicated improvements in both populations: -40.7 mg/dL and -26.7 mg/dL, respectively.

Results for the secondary endpoint supported the primary endpoint, with an improvement in dysglycaemia category from baseline to Week 48 in 37.7% of patients.

These results indicate that ELX/TEZ/IVA does at least not deteriorate glucose tolerance in CF subjects with IGT or CFRD.

Subgroup analysis by age (i.e. adolescents 12-18 years vs. adults ≥18 years) have not been presented. In line with previous procedures for ELX/TEZ/IVA, it is acceptable to pool results for adolescents and adults and no separate analysis per age group is requested.

Safety

No new safety concerns were identified. Almost all patients (97.1%) experienced at least 1 adverse event (AE). Most AEs were mild or moderate in severity. Ten (14.5%) patients had severe AEs, which were all grade 3 events reported for one or two patients each. Six (8.7%) subjects had serious adverse events (SAEs), none of which were considered to be related to study drug. There were no life-threatening AEs or deaths. The data related to AEs of special interest rash events and transaminase elevations were consistent with prior experience. ELX/TEZ/IVA was generally safe and well tolerated with a low rate of treatment discontinuations. Overall, the AEs were mostly consistent with common manifestations of CF disease or with the known safety profile of ELX/TEZ/IVA.

Conclusion

Based on final results of Study 117, glucose tolerance in CF patients aged 12 years and older with IGT or CFRD is at least not deteriorated by treatment with ELX/TEZ/IVA. No new safety concerns were identified.The benefit risk of ELX/TEZ/IVA remains positive and no update to the product information is deemed necessary.

3. Rapporteur's overall conclusion and recommendation

The benefit-risk evaluation of Kaftrio remains positive.

☒ **Fulfilled:**

☐ **Not fulfilled:**

Based on the data submitted, the MAH should provide results from all predefined other endpoints of Study 117 as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

Major objections

None

Other concerns

Clinical

1. The Applicant is requested to present results for the following predefined other endpoints: change from baseline in: CGM parameter MAGE in patients with CFRD at Week 48, HbA1C, insulin use, post-OGTT diabetes-related biomarkers, biomarkers of inflammation, biomarkers of pancreatic function and post-OGTT incretin levels.

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

MAH responses to Request for supplementary information

Major objections

N/A

Other concerns

Clinical

1. The Applicant is requested to present results for the following predefined other endpoints: change from baseline in: CGM parameter MAGE in patients with CFRD at Week 48, HbA1C, insulin use, post-OGTT diabetes-related biomarkers, biomarkers of inflammation, biomarkers of pancreatic function and post-OGTT incretin levels.

Applicant's response

The requested endpoints were exploratory analyses. There is limited information available relating to how these parameters change in a cystic fibrosis (CF) population with abnormal glucose metabolism, and none of these endpoints are validated or utilized in routine clinical practice for the diagnosis or

treatment/management of CF-related diabetes (CFRD; based on current/accepted CFRD guidelines[1]). The interpretability of these exploratory analyses is limited; therefore, they were not included in the clinical study report.

Assessment of the response

The clarification provided by the Applicant is accepted.

Conclusion

Issue resolved.

[1] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010;33(12):2697-708