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/P46/009

Note

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

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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 initially obtained a marketing authorisation 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 are homozygous for patients 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 the final study results of Study VX20-445-126 (Study 126). This was a Phase 3b, open-label study designed to evaluate additional endpoints related to quality of life beyond those evaluated in the pivotal studies (i.e., cough, daily activity, and sleep quality) using wearable technology in CF patients aged 12 years and older.

The MAH stated that Study VX20-445-126 (Study 126) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study VX20-445-126, 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 authorised 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(s) for: Study VX20-445-126 (Study 126), a Phase 3b Open-label Study Evaluating the Effects of ELX/TEZ/IVA on Cough and Physical Activity in CF Subjects 12 Years of Age and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF).

### 2.3.2. Clinical study

Study VX20-445-126 (Study 126)

Description

Study VX20-445-126 (Study 126) was a Phase 3b Open-label Study Evaluating the Effects of

ELX/TEZ/IVA on Cough and Physical Activity in CF Subjects 12 Years of Age and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF).

The study design is shown in Figure 1.

Figure 1. Study 126 Design
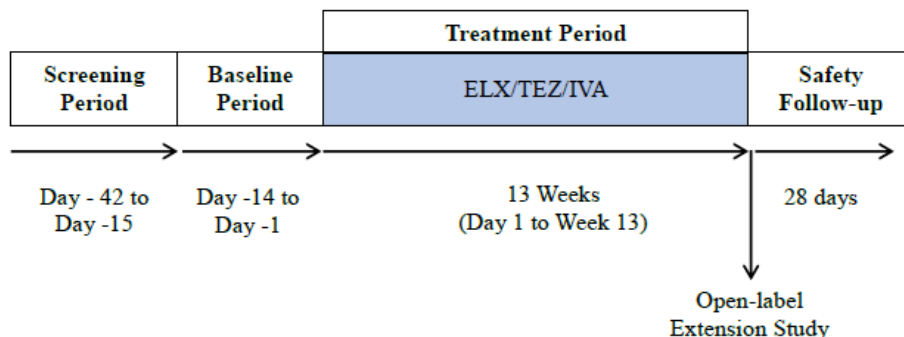
Source: Study 126 CSR/Figure 9-1
ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Notes: Eligible subjects were offered the opportunity to enroll in an open-label extension safety study evaluating ELX/TEZ/IVA.

Methods

Study participants

The study included patients aged 12 years and older with F/MF *CFTR* genotype, stable CF disease and ppFEV1 ≥30% and ≤90%. Key eligibility criteria are shown in Table 1.

Table 1. Key eligibility criteria Study 126

Inclusion Criteria	Exclusion Criteria
• 12 years of age or older • F/MF *CFTR* genotype • Forced expiratory volume in 1 second (FEV$_1$) value ≥30% and ≤90% of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI][1]) at the Screening Visit • Stable CF disease as judged by the investigator • Remain on stable CF treatment regimen (other than CFTR modulators) through completion of study participation	• History of any illness or clinical condition that could confound the results of the study or pose an additional risk in administering study drug(s) to the subject (including non-ambulatory status) • Any protocol-defined laboratory values at screening that would interfere with the study or pose an undue risk • An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before first dose of study drug • Lung infection 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 • Ongoing or prior participation in an investigational drug study within 28 days of the Screening Visit • Use of protocol-defined restricted medications within specified duration before the first dose of study drug (including CFTR modulators within 6 months before start of the baseline period) • Pregnant or breast-feeding females • Subject or close relative of the subject directly involved with the conduct of the study at that site

Sources: Study 126 Protocol Version 1.0/Section 8.1, Section 8.2, and Section 9.4.
CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; F/MF: heterozygous for *F508del* and a minimal function mutation; FEV$_1$: forced expiratory volume in 1 second; GLI: Global Lung Function Initiative

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 with a fat-containing meal or snack.

During the Treatment Period, patients were to be administered ELX/TEZ/IVA for approximately 13 weeks.

Objective

The study objective was to evaluate the effects of ELX/TEZ/IVA on cough and physical activity using wearable technology.

Outcomes/endpoints

Primary endpoint

The percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12.

Secondary endpoint

Absolute change from baseline in total step count per day to the average of Week 8 through Week 12.

Other endpoints

- Absolute change from baseline in activity patterns to the average of Week 8 through Week 12, as described by:

    o Time spent per day above sedentary physical activity (≥1.5 metabolic equivalents [METs])

    o Time spent per day in moderate-to-vigorous physical activity (MVPA; ≥3.0 METs)

    o Time spent per day in continuous walking bouts

    o Total activity count per day

- Absolute change from baseline in best 6-minute effort (B6ME) per day to the average of Week 8 through Week 12.

- Absolute change from baseline in preferred cadence to the average of Week 8 through Week 12.

- Absolute change from baseline in sleep quality to the average of Week 8 through Week 12, as described by:

    o Sleep efficiency

    o Sleep latency

    o Sleep duration per day

    o Number of nocturnal awakenings per day

- Absolute change from baseline in Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) scores to the average of Week 8 and Week 12.

- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) vitality and physical functioning domain scores to the average of Week 8 and Week 12.

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

Sample size

Assuming a standard deviation of 1 for the log ratio of cough frequency post-baseline versus baseline, a sample size of approximately 100 subjects will provide 95% confidence intervals (which represents the estimation precision) as shown in Table 2 at various observed percent reductions in cough frequency (30%, 40%, and 50%), after accounting for 20% missing. Note: percent reduction equals 100% × (1- ratio of cough frequency post-baseline vs. baseline).

Table 2. 95% Confidence Intervals for Percent Reduction in Cough Frequency per day from Baseline

Percent reduction in cough frequency	30%	40%	50%
95% Confidence Intervals	(13%, 44%)	(25%, 52%)	(38%, 60%)

30%, 40%, 50% percent reduction corresponds to ratio of 0.7, 0.6 and 0.5 in cough frequency (post-baseline vs. baseline), respectively.

Randomisation and blinding (masking)

Not applicable, as this is an open-label single arm trial. However, subjects and their parent/legal guardian were not informed of their study-related spirometry, cough, activity, and sleep quality (from the actigraphy sensor) results during the Treatment Period.

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 received at least 1 dose of study drug. The FAS was used in efficacy analyses.

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

Efficacy analyses

For efficacy analyses, baseline cough was defined as the geometric mean of valid cough measurements before the first dose of study drug. Baseline step count, other activity endpoints, and other sleep endpoints measured by actigraphy were defined as the average of valid weekly interval measurements prior to the first dose of study drug. Baseline PSQI, ESS, and CFQ-R were defined as the Day 1 assessment.

The method of analysis for the primary and secondary endpoints are shown in Table 3.

Table 3. Key efficacy endpoints and methods

Endpoint (Data set/Analysis Set)	Method of Analysis
Primary Efficacy Endpoint	

Percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12	• Mixed-effects model for repeated measures (MMRM) with change from baseline on the log scale as the dependent variable
	   ○ Estimated using restricted maximum likelihood
	   ○ Kenward-Roger approximation used to estimate the denominator degrees of freedom for the F-test for fixed effects
	   ○ Unstructured covariance structure was used to model within-subject errors
	• Percent reduction was calculated as 100% × (1-exponential form of LS mean change at the average of Weeks 8 through 12 on the natural log scale) with 2-sided 95% CI
	• Line plot
	• Summary statistics of raw values (geometric mean, geometric SD)
	• Similar analyses for daytime and overnight cough frequency per hour

Secondary Efficacy Endpoint	

Absolute change from baseline in total step count per day to the average of Week 8 through Week 12	• MMRM model
	   ○ Change from baseline at each post-baseline interval as the dependent variable
	
	   ○ Weekly intervals as fixed effects and baseline total step count per day as a covariate
	• Estimated LS mean change and 2-sided 95% CI
	• Line plot
	• Summary statistics (n, mean, SD, median, minimum, and maximum)

Multiplicity control - No multiplicity adjustment was performed.

Interim analysis – No interim analysis was planned.

Handling of missing values/censoring/discontinuations – Missing data were not imputed.

Results

Participant flow

A total of 81 patients enrolled and received at least 1 dose of study drug, and 79 (97.5%) patients completed study drug treatment (Table 4). Two (2.5%) patients discontinued treatment due to adverse events (AEs); one (1.2%) of these patients also discontinued the study.

Table 4. Subject disposition (All Subjects Set)

Disposition	ELX/TEZ/IVA n (%)
All Subjects Set	82
Full Analysis Set	81
Safety Set	81
Never dosed	1
Completed treatment	79 (97.5)
Discontinued treatment	2 (2.5)
Reason for discontinuation of treatment	
Adverse event	2 (2.5)
Completed study	80 (98.8)
Discontinued study	1 (1.2)
Reason for discontinuation from study	
Adverse event	1 (1.2)
Rollover to the open-label study	
Yes	55 (67.9)
No	26 (32.1)

Source: Table 14.1.1
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor
Notes: All Subjects Set is defined as all subjects who were enrolled. Full Analysis Set is defined as all enrolled subjects who carry the intended CFTR allele mutations and have received at least 1 dose of study drug. Safety Set is defined as all subjects who have received at least 1 dose of study drug. Percentages were calculated relative to the number of subjects in the Full Analysis Set. Number of subjects who completed the study included those who completed the Week 13 Visit and either entered an open-label extension study within 28 days or completed the Safety Follow-up Visit.

Recruitment

Study initiation: 12 October 2021 (date first eligible subject signed the informed consent form)

Study completion: 26 July 2022 (date last subject completed the last visit)

The study was conducted at 18 sites in Australia, Belgium, Canada and Spain.

Conduct of study

Protocol amendments

There were no amendments to Version 1.0 of the protocol and no changes to the statistical analysis plan.

Protocol deviations

A total of 14 patients had 18 important protocol deviations, mostly related to study conduct/procedures (n=5), prohibited concomitant medications (n=3) and eligibility criteria (n=3).

Baseline data

All 81 patients were White, 3.7% of patients were also Hispanic or Latino and 54.3% were male. The median (min, max) age at baseline was 24.6 (12.2, 45.2) years (Table 5).

Table 5. Patient demographics (FAS)

Demographic	ELX/TEZ/IVA N = 81
Sex, n (%)	
Male	44 (54.3)
Female	37 (45.7)
Childbearing potential[a], n (%)	
Yes	37 (100.0)
No	0
Age at baseline (years)	
n	81
Mean (SD)	25.7 (9.6)
Median	24.6
Min, max	12.2, 45.2
Age category at baseline, n (%)	
<18 years	24 (29.6)
≥18 years	57 (70.4)
Race, n (%)	
White	81 (100.0)
Ethnicity, n (%)	
Hispanic or Latino	3 (3.7)
Not Hispanic or Latino	78 (96.3)
Country, n (%)	
Australia	36 (44.4)
Belgium	31 (38.3)
Canada	7 (8.6)
Spain	7 (8.6)

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 is defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. If a subject is reported to have multiple races, then the subject is counted for each race reported.
a   Female n is the denominator.

At baseline, the geometric mean cough frequency per day was 241.3 coughs per day, and the mean step count was 5278.63 steps per day. The median BMI was 21.05 kg/m^2 and the median ppFEV1 was 69.2 percentage points at baseline (Table 6).

Table 6. Baseline characteristics (FAS)

Characteristic	ELX/TEZ/IVA N = 81
Weight (kg)	
n	81
Mean (SD)	59.5 (12.2)
Median	59.0
Min, max	35.0, 96.0
Height (cm)	
n	81
Mean (SD)	166.4 (9.3)
Median	166.0
Min, max	144.0, 192.0
BMI (kg/m²)	
n	81
Mean (SD)	21.34 (3.03)
Median	21.05
Min, max	15.07, 31.35
ppFEV₁ category at baseline, n (%)	
<30	0
≥30 to <40	4 (4.9)
≥40 to <70	37 (45.7)
≥70 to ≤90	40 (49.4)
>90	0
ppFEV₁ at baseline	
n	81
Mean (SD)	67.8 (14.3)
Median	69.2
Min, max	37.7, 89.7
Prior use of dornase alfa*, n (%)	
Yes	68 (84.0)
No	13 (16.0)
Prior use of azithromycin*, n (%)	
Yes	41 (50.6)
No	40 (49.4)
Prior use of inhaled antibiotic*, n (%)	
Yes	34 (42.0)
No	47 (58.0)
Prior use of any bronchodilator*, n (%)	
Yes	70 (86.4)
No	11 (13.6)
Prior use of any inhaled bronchodilator*, n (%)	
Yes	70 (86.4)
No	11 (13.6)
Prior use of any inhaled hypertonic saline*, n (%)	
Yes	52 (64.2)
No	29 (35.8)
Prior use of any inhaled corticosteroids*, n (%)	
Yes	47 (58.0)
No	34 (42.0)

Source: Table 14.1.4

BMI: body mass index; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total
   sample size; ppFEV₁: percent predicted forced expiratory volume in 1 second; SD: standard deviation; TEZ:
   tezacaftor

Note: Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the
   Treatment Period. *: Includes medications administered during 56 days before the first dose of study drug.

Number analysed

The final number of patients in each analysis set is shown in Table 7.

Table 7. Patient disposition

Disposition	ELX/TEZ/IVA n (%)
All Subjects Set	82
Full Analysis Set	81
Safety Set	81

Efficacy results

<u>Primary endpoint</u> – *The percent reduction from baseline in cough frequency (cough events per day) to the average of Week 8 through Week 12.*

Treatment with ELX/TEZ/IVA resulted in a 91.7% percent reduction (95% CI: 89.2%, 93.6%) in cough frequency per day at the average of Week 8 through Week 12 (Table 8; Figure 2).

Table 8. MMRM analysis: percent reduction from baseline in cough frequency per day at average of week 8 through week 12 (FAS)

	ELX/TEZ/IVA N = 81
Baseline	
n	81
Log-transformed mean (SD)	5.5 (1.2)
Geometric mean (GSD)	241.3 (3.4)
Average of Week 8 through Week 12	
n	80
LS mean change on natural log scale (SE)	-2.5 (0.13)
Geometric mean ratio (GSE)	0.083 (1.140)
Percent reduction (%)	91.7
95% CI of percent reduction (%)	(89.2, 93.6)

Source: Table 14.2.1.1

ELX: elexacaftor; GSD: geometric standard deviation; GSE: geometric standard error; IVA: ivacaftor; MMRM: mixed-effects model of repeated measures; n: size of subsample; N: total sample size; SD: standard deviation; SE: standard error; TEZ: tezacaftor

Notes: The measurement was considered as valid if the recording duration was at least 10 hours while awake during the 24-hour measurement period. Baseline value was defined as the geometric mean of valid cough measurements before the first dose of study drug. Percent reduction and 95% CIs were calculated by transforming the estimated mean change in log-transformed values (100×[1 - exponential form of LS mean]). If the number of coughs per day was zero at any visit, 0.5 was added in order to ensure a non-zero number for any log transformations and geometric mean calculations. MMRM included data from all available visits up to Week 12, with change from baseline on the natural log scale as dependent variable, visit as fixed effect, and baseline cough frequency on the natural log scale as covariate. Denominator degrees of freedom were estimated using the Kenward-Roger approximation. An unstructured covariance structure was used to model the within-subject errors.

Figure 2. MMRM analysis: percent change from baseline in cough frequency per day at each visit up to week 12 (FAS)
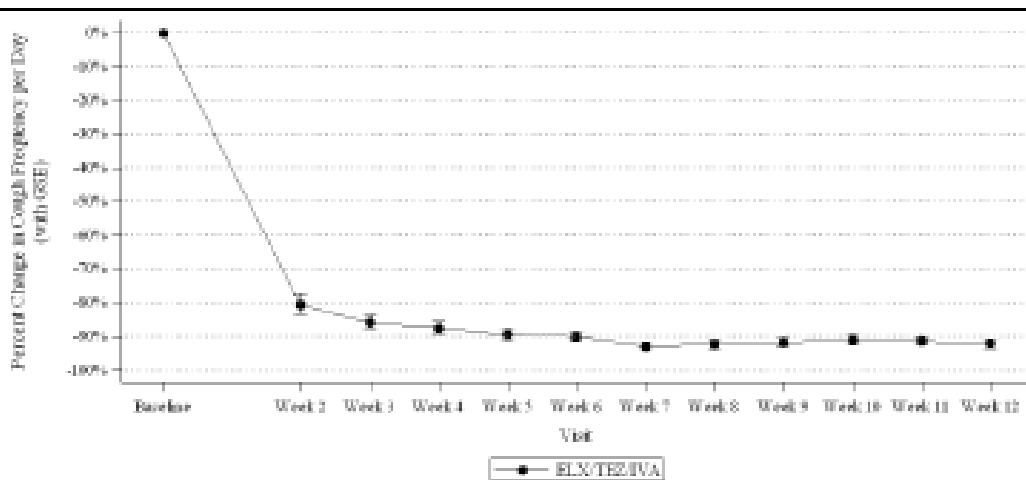
Source: Figure 14.2.1.1
ELX: elexacaftor; GSE: geometric standard error; IVA: ivacaftor; MMRM: mixed-effects model of repeated measures; TEZ: tezacaftor
Notes: The measurement was considered as valid when the recording duration was at least 10 hours while awake during the 24-hour measurement period. Baseline value was defined as the geometric mean of valid cough measurements before the first dose of study drug. Percent change and GSE were calculated by transforming (exponential-transform) the estimates based on log transformed values. When the number of coughs per day was zero at any visit, 0.5 was added in order to ensure a non-zero number for the percent change calculation. MMRM included data from all available visits up to Week 12, with change from baseline on the natural log scale as dependent variable, visit as fixed effect, and baseline on the natural log scale cough frequency as covariate. Denominator degrees of freedom were estimated using the Kenward-Roger approximation. An unstructured covariance structure was used to model the within-subject errors.

Secondary endpoint – *Absolute change from baseline in total step count per day to the average of Week 8 through Week 12.*

Treatment with ELX/TEZ/IVA resulted in an improvement in total step count per day at average of Week 8 through Week 12, with an LS mean absolute change from baseline of 637.56 steps (95% CI: 298.16, 976.96).

Exploratory endpoints

The absolute change from baseline in activity patterns to the average of Week 8 through Week 12, as measured by the actigraphy watch is summarised in Table 9. The other endpoints 'absolute change from baseline in best 6-minute effort (B6ME) per day to the average of Week 8 through Week 12' and 'absolute change from baseline in preferred cadence to the average of Week 8 through Week 12' are shown in Table 9 as well. For most activity pattern endpoints, scores improved with ELX/TEZ/IVA treatment or remained more or less similar.

Table 9. Change from baseline in activity pattern endpoints (FAS)

Time Spent Above Sedentary Physical Activity per Day (Minutes)	
Baseline	
n	81
Mean (SD)	452.43 (100.90)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	18.08 (55.87)
95% CI of Mean[a]	5.65, 30.52
Time Spent in Moderate-to-Vigorous Physical Activity per Day (Minutes)	
Baseline	
n	81
Mean (SD)	115.39 (48.53)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	18.36 (52.30)
95% CI of Mean[a]	6.72, 30.00
Time Spent Walking Continuously for ≥5 Minutes (Minutes)	
Baseline	
n	81
Mean (SD)	10.59 (11.83)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	0.94 (10.61)
Total Activity Counts per Day (Count)	
Baseline	
n	81
Mean (SD)	4121630.90 (1123502.01)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	193731.49 (653118.54)
95% CI of Mean[a]	48387.08, 339075.90
Best 6-Minute Effort (B6ME) per Day (Count)	
Baseline	
n	81
Mean (SD)	396.84 (119.39)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	20.44 (91.97)
Preferred Cadence (Steps per Minute)	
Baseline	
n	81
Mean (SD)	106.41 (4.84)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	0.37 (4.10)

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SD: standard deviation; TEZ: tezacaftor

Notes: The daily assessment was considered as valid if there were at least 10 hours of valid wear data while awake on that day. For each weekly interval, the value per day was calculated by averaging valid daily assessments in that week, provided that there were valid daily assessments on at least 3 weekdays and 1 weekend day. Baseline value is defined as the average of valid weekly interval measurements before the first dose of study drug.

[a] 95% CI were estimated as part of an ad hoc analysis.

The absolute <u>change from baseline in sleep quality</u> to the average of Week 8 through Week 12, as measured by the actigraphy watch is shown in Table 10. There were no notable changes in the validated sleep quality endpoints.

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Table 10. Absolute change from baseline in sleep quality (FAS)

	ELX/TEZ/IVA N = 81
Sleep Efficiency (Percent)	
Baseline	
n	81
Mean (SD)	80.69 (9.89)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	-0.15 (4.53)
Sleep Onset Latency (Minutes)	
Baseline	
n	81
Mean (SD)	6.95 (4.68)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	-0.40 (4.80)
Total Sleep Time (Minutes)	
Baseline	
n	81
Mean (SD)	389.74 (53.10)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	-5.42 (30.90)
Number of Awakenings After Sleep Onset (Count)	
Baseline	
n	81
Mean (SD)	5.80 (2.22)
Absolute change at Average of Week 8 through Week 12	
n	80
Mean (SD)	0.03 (1.30)

Source: Table 14.2.3.2
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SD: standard deviation; TEZ: tezacaftor
Notes: The nightly assessment was considered as valid if there were at least 3 hours of defined sleep on that night.
For each weekly interval, the average value was calculated based on valid nightly assessments in that week, provided that there were valid nightly measures on at least 3 weekday nights and 1 weekend night. Baseline value is defined as the average of valid weekly interval measurements before the first dose of study drug.

The absolute change from baseline in Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) scores to the average of Week 8 and Week 12 is shown in Table 11. The decrease in mean scores suggests improvements in sleep quality (PSQI) and daytime sleepiness (ESS) with ELX/TEZ/IVA treatment.

Table 11. Absolute change from baseline in PSQI and ESS score (FAS)

	ELX/TEZ/IVA N = 81
Pittsburgh Sleep Quality Index: Global Score	
Baseline	
n	76
Mean (SD)	6.8 (3.7)
Absolute change at Average of Week 8 and Week 12	
n	67
Mean (SD)	-1.8 (2.8)
95% CI of Mean[a]	-2.5, -1.1
Epworth Sleepiness Scale	
Baseline	
n	75
Mean (SD)	6.6 (4.1)
Absolute change at Average of Week 8 and Week 12	
n	66
Mean (SD)	-2.1 (3.4)
95% CI of Mean[a]	-2.9, -1.3

ELX: elexacaftor; ESS: Epworth Sleepiness Scale; IVA: ivacaftor; n: size of subsample; N: total sample size; PSQI: Pittsburgh Sleep Quality Index; SD: standard deviation; TEZ: tezacaftor

Notes: Baseline value is defined as the assessment on Day 1. For ESS, data from the 'Children and Adolescents' version and 'Adults' version were pooled.

[a]   95% CI were estimated as part of an ad hoc analysis.

The absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) vitality and physical functioning domain scores to the average of Week 8 and Week 12 is shown in Table 12. The scores increased for both domains, suggesting better health related quality of life with ELX/TEZ/IVA treatment.

Table 12. Absolute change from baseline in CFQ-R physical and vitality domain scores (FAS)

	ELX/TEZ/IVA N = 81
Physical Domain	
Baseline	
n	78
Mean (SD)	67.6 (26.4)
Absolute change at Average of Week 8 and Week 12	
n	72
Mean (SD)	21.5 (23.9)
Vitality Domain	
Baseline	
n	70
Mean (SD)	48.8 (21.6)
Absolute change at Average of Week 8 and Week 12	
n	65
Mean (SD)	21.1 (20.2)

Source: Table 14.2.3.5

CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SD: standard deviation; TEZ: tezacaftor

Notes: Baseline value is defined as the assessment on Day 1. Physical domain data from the 'Children Ages 12 and 13' version and the 'Adolescents and Adults' version were pooled. Vitality domain applies to data from the 'Adolescents and Adults' version only.

Safety results

Safety was analysed in 81 patients of Study 126, 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 12.2 weeks (5.7, 13.1; Table 13).

Table 13. Summary of exposure (Safety Set)

	ELX/TEZ/IVA N = 81
Total exposure (patient weeks)	986.6
Exposure duration (weeks)	
n	81
Mean (SD)	12.2 (0.8)
Median	12.1
Min, max	5.7, 13.1
Exposure duration by interval, n (%)	
>0 to ≤2 weeks	0
>2 to ≤4 weeks	0
>4 to ≤8 weeks	1 (1.2)
>8 to ≤12 weeks	36 (44.4)
>12 weeks	44 (54.3)

Source: Table 14.1.7
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SD: standard deviation; TEZ: tezacaftor
Notes: Total exposure is 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 (92.6%) experienced at least 1 adverse event (AE; Table 14). All AEs were mild or moderate in severity. Two patients (2.5%) had serious adverse events (SAEs), both of which were considered possibly related to study drug. There were no life-threatening AEs or deaths.

Table 14. Overview of AEs (Safety Set)

Category	ELX/TEZ/IVA N = 81 n (%)
Number of AEs (total)	275
Subjects with any AEs	75 (92.6)
Subjects with AEs by strongest relationship	
Not related	21 (25.9)
Unlikely related	16 (19.8)
Possibly related	28 (34.6)
Related	10 (12.3)
Subjects with AEs by maximum severity	
Grade 1/Mild	47 (58.0)
Grade 2/Moderate	28 (34.6)
Grade 3/Severe	0
Grade 4/Life-threatening	0
Grade 5/Death	0
Subjects with AEs leading to study drug discontinuation	2 (2.5)
Subjects with AEs leading to study drug interruption	8 (9.9)
Subjects with Grade 3/4/5 AEs	0
Subjects with related AEs[a]	38 (46.9)
Subjects with SAEs	2 (2.5)
Subjects with related SAEs[a]	2 (2.5)
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 was 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, 6. Missing. 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. 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 has missing severity, then the subject was summarized in the "Missing" category.
[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 ≥5% of patients are summarised by preferred term (PT) in Table 15. The most common adverse events were headache (17.3%), COVID-19 (16%), nasopharyngitis (16%) and diarrhoea (13.6%).

Table 15. AEs occurring in at least 5% of patients by PT (Safety Set)

Preferred Term	ELX/TEZ/IVA N = 81 n (%)
Subjects with any AEs	75 (92.6)
Headache	14 (17.3)
COVID-19	13 (16.0)
Nasopharyngitis	13 (16.0)
Diarrhoea	11 (13.6)
Abdominal pain	8 (9.9)
Oropharyngeal pain	8 (9.9)
Abdominal pain upper	7 (8.6)
Upper respiratory tract infection	7 (8.6)
Cough	6 (7.4)
Nasal congestion	5 (6.2)
Rash	5 (6.2)

Source: Table 14.3.1.3
AE: adverse event; 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 (Overall or PT) was counted only once in that category.

Severity of adverse events

All AEs were mild (58%) or moderate (34.6%) in severity. No patients had severe AEs, life-threatening AEs, or an AE that resulted in death.

Relationship of adverse events

There were 10 (12.3%) patients with related AEs and 28 (34.6%) patients with possibly related AEs. AEs at least possibly related to study drug were most frequently reported for system organ class (SOC) gastro-intestinal disorders (19.8%), respiratory, thoracic and mediastinal disorders (9.9%) and skin- and subcutaneous tissue disorders (9.9%).

The most common (>3%) at least possibly related AEs were diarrhoea (4.9%), rash (4.9%), headache (4.9%), abdominal pain (3.7%), abdominal pain upper (3.7%) and sputum increased (3.7%).

Deaths and other serious adverse events

There were no life-threatening AEs or deaths.

Two patients (2.5%) had serious adverse events (SAEs; anxiety and pancreatitis), both of which were assessed by the investigator as moderate in severity and possibly related to study drug. The SAE of anxiety resulted in study drug discontinuation and the SAE was considered resolved.

Study drug discontinuation

There were 2 (2.5%) patients with AEs resulting in discontinuation. One patient (1.2%) discontinued study drug due to a SAE of anxiety, and one patient discontinued study drug (IVA only) due to AEs of ALT and AST increased.

Adverse events of special interest

Elevated transaminase events

Three (3.7%) patients had elevated transaminase events, all of which were assessed by the investigator as mild or moderate in severity. One (1.2%) patient had an elevated transaminase event that led to study drug interruption and one (1.2%) subject had an elevated transaminase event that led to treatment discontinuation.

<u>Rash events</u>

Seven (8.6%) patients had at least 1 of any rash event. All rash events were mild or moderate in severity; none were serious. Three subjects 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, 3 (8.1%) female patients and 4 (9.1%) male subjects had rash events. Of the female patients who had rash events, all 3 (21.4%) had concomitant use of hormonal therapy.

Clinical laboratory evaluation

<u>Chemistry</u>

Elevated transaminase events - are described above.

Creatinine kinase (CK) –AEs of blood CK increased were reported in 1 (1.2%) patient.

Other chemistry parameters – There were no clinically significant findings in mean value in other non-LFT chemistry parameters.

<u>Vital signs</u>

There were no trends observed in the vital signs or ECG parameters. No patients had AEs related to ECG findings or relevant cardiac disorders.

2.3.3. Discussion on clinical aspects

Design and conduct

With this article 46 procedure, the MAH presented the final study results of Study VX20-445-126 (Study 126). This was a Phase 3b, open-label study designed to evaluate additional endpoints related to quality of life beyond those evaluated in the pivotal studies (i.e., cough, daily activity, and sleep quality) using wearable technology in CF patients aged 12 years and older. Study 126 is a stand-alone study. No changes to the current product information for ELX/TEZ/IVA have been proposed.

The single-arm trial design and lack of definition of a minimal important clinical difference (MCID) in CF for the main clinical endpoints hamper the interpretation of obtained results.

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

Results

Efficacy

A total of 81 patients enrolled and received at least 1 dose of study drug, and 79 (97.5%) patients completed study drug treatment. The median age at baseline was 24.6 years, with 24 patients (29.6%) <18 years of age. At baseline, the geometric mean cough frequency per day was 241.3 coughs per day, and the mean step count was 5278.63 steps per day.

Treatment with ELX/TEZ/IVA in CF subjects 12 years of age and older with F/MF genotypes resulted in a 91.7% (95% CI: 89.2%, 93.6%) reduction in cough frequency from baseline to the average of Week 8 through Week 12. This resembles a substantial reduction from approximately 24 coughs per hour to less than 1 per hour, which is considered clinically relevant.

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.

Treatment with ELX/TEZ/IVA in CF subjects 12 years of age and older with F/MF genotypes improved the secondary endpoint total step count, with an LS mean absolute change from baseline 637.56 steps (95% CI: 298.16, 976.96). It is acknowledged that it is uncertain whether this improvement is clinically relevant, as the minimal clinically important difference (MCID) for step count has been established in a chronic obstructive respiratory disease (COPD) but not, to date, in CF. The differences between the two populations, e.g. in mean age and concomitant diseases, do not allow for an interpretation of the relevance based on the validation in COPD patients.

The other endpoints showed limited (activity patterns) or no notable changes (sleep quality endpoints) in the quality of life endpoints as measured by the actigraphy watch. In contrast, the patient reported outcomes as measured by questionnaires (sleep related questionnaire PSQI and ESS; and the vitality and physical functioning domains of CFQ-R) suggest some improvements with ELX/TEZ/IVA treatment. However, the study was not designed to draw firm conclusions based on these exploratory endpoints.

Safety

No new safety concerns were identified. Almost all patients (92.6%) experienced at least 1 adverse event (AE). All AEs were mild or moderate in severity. Two patients (2.5%) had serious adverse events (SAEs), both of which were considered possibly 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 126, treatment with ELX/TEZ/IVA reduced the cough frequency and seems to increase the activity as measured by step count. The clinical relevance of most quality-of-life endpoints, including step count, is uncertain as no MCID was defined. No new safety concerns were identified. Overall, it is agreed with the Applicant that 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:**

No regulatory action required.

☐ **Not fulfilled:**

4. Request for supplementary information

Not applicable.