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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/P46/012

Note

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

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

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1. Introduction

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

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

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

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

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

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

Table 1 Dosing recommendation for patients aged 6 years and older

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

The MAH now submitted the results of Study VX18-445-113 ("Study 113") as per requirement of Article 46 of the "Paediatric Regulation" (EC) 1901/2006. Study 113 is a Phase 3, multicenter, open-label study (OLS) in CF subjects 12 years of age and older, homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and a minimal function mutation (F/MF genotypes), who transferred from

Study VX17-659-105 (Study 659-105). The primary objective was to evaluate the long-term safety and tolerability of ELX/TEZ/IVA.

The MAH stated that Study VX18-445-113 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The following tablets were used in the study:

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

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study VX18-445-113, a Phase 3, multicenter, open-label study (OLS) in CF subjects 12 years of age and older, homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and a minimal function mutation (F/MF genotypes), who transferred from Study VX17-659-105 (Study 659-105).

2.3.2. Clinical study

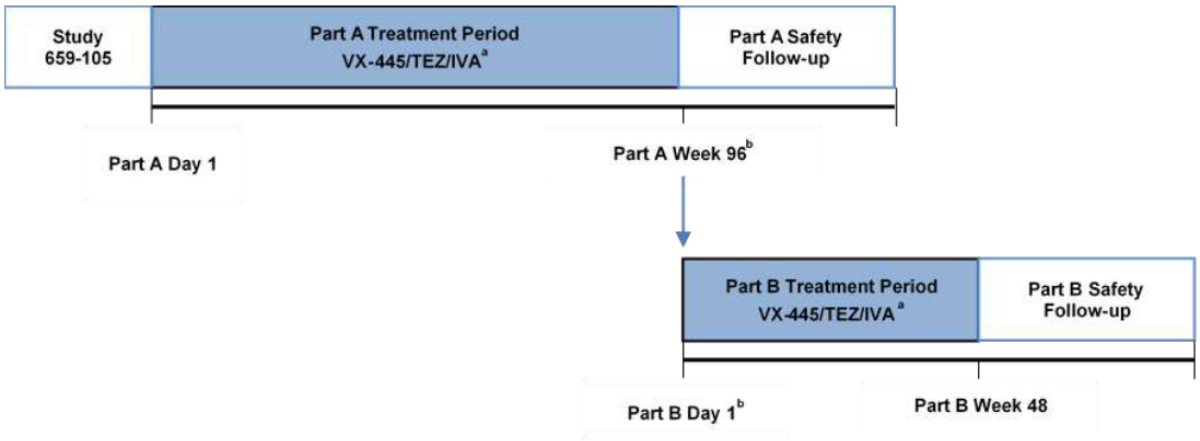
Study VX18-445-113

Description

Study 113 was a Phase 3, multicenter, open-label study for subjects transferred from Study 659-105, a Phase 3 Vertex study investigating VX-659/TEZ/IVA and met eligibility criteria (Figure 1). Subjects in certain countries who completed Part A had the opportunity to participate in Part B.

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

Figure 1 Study Design



Source: Study 113 CSR/Figure 9-1
ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Figure is not drawn to scale. VX-445 refers to ELX.

[a] All subjects received ELX 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h.

[b] Subjects whose Part B Day 1 Visit was on the same day as the Part A Week 96 Visit did NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 96 Visit. Subjects whose Part B Day 1 and Part A Week 96 Visits did not coincide completed all assessments specified for the Part A Week 96 AND Part B Day 1 Visits.

The study period was from 09 August 2019 until 14 December 2022.

CHMP comment

Countries that also offered Part B of this study seem to be AU, CA, ES, and PO. Part B was added in these countries with Versions 1.5 to 1.8 of the Clinical Study Protocol (08 March 2021) (see Conduct of Study below). It is not completely understood why Part B was only accessible for subjects in these countries. However, considering the sufficiently long treatment period of Part A, the fact that only safety was assessed in Part B, and most patients discontinued Part B due to commercial availability of Kaftrio, this issue is not further pursued.

Methods

Study participants

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

Key eligibility criteria are shown in Table 2.

Table 2 Key Eligibility Criteria in Study 113

Inclusion Criteria	Exclusion Criteria

• Current participation in Study 659-105, which was defined as one of the following:
  ○ On study drug treatment in Study 659-105 as of the day prior to the Day 1 Visit in this study
  ○ On study drug interruption in Study 659-105 as of the day prior to the Day 1 Visit in this study
• Subjects who permanently discontinued VX-659/TEZ/IVA in Study 659-105 for any reason other than enrolling into this study were not eligible
• Willing to remain on a stable CF regimen through completion of study participation
	• History of any comorbidity that could confound the results of the study or pose an additional risk in administering study drug to the subject
	• Pregnant or breast-feeding females
	• History of drug intolerance in Study 659-105 that would pose an additional risk to the subject
	• Current participation in an investigational drug trial (other than Study 659-105)

Sources: Study 113 Protocol/Sections 8.1 and 8.2
CF: cystic fibrosis; IVA: ivacaftor; TEZ: tezacaftor

CHMP comment

Study 659-105 investigated the triple combination of VX-659 (a third generation CFTR corrector), TEZ and IVA. It was a 96-week open-label extension (OLE) study, which assessed the safety and tolerability of the triple combination in subjects who completed the randomised control parent studies VX17-659-102 or VX17-659-103. Patients participating in study 659-105 were able to roll over to study 105, in which VX-659 was replaced by Elexacaftor (VX-445).

Eligibility criteria are acceptable.

Treatments

All subjects received two FDC tables of ELX/TEZ/IVA in the morning and one IVA tablet in the evening.

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

CHMP comment

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

Objective(s)

Primary objective:

To evaluate the long-term safety and tolerability of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA).

Outcomes/endpoints

Primary endpoint:

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

Other endpoint:

Sweat chloride (SwCl)

Sample size

The primary objective of the study is the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. This is an open-label study that enrolled subjects previously enrolled in Study 659-105 and met the Study 445-113 eligibility criteria.

Over 400 subjects were planned to be enrolled in this study. With this number of subjects exposed to ELX/TEZ/IVA treatment, AEs by Preferred Term (PT) that occur with a frequency of >1% will be ruled out with 95% confidence, when 0 events are observed in that PT.

CHMP comment

The primary endpoint of safety and tolerability after long-term treatment is appropriate for an open-label extension study. There were no secondary endpoints. However, SwCl was also assessed. It is unclear why the Applicant chose only SwCl and not (also) the preferred CF outcome measure ppFEV1.

A sample size of 400 subjects for Part A is also considered acceptable.

Randomisation and blinding (masking)

N/A

Statistical Methods

Analysis sets

The following analysis sets were defined:

- **All Subjects Set:** all subjects who were enrolled (defined as subject having data in the clinical database) in this study.
- **Safety Set**: all subjects who have received at least 1 dose of study drug in this study.

Efficacy analyses

N/A

Safety analyses

The primary objective of the study was the evaluation of the long-term safety and tolerability of ELX/TEZ/IVA. Safety analyses were planned to be summarised separately for Parts A and B. Part A safety analyses are based on the Treatment Emergent (TE) Period for Part A for subjects in the Safety Set for Part A. Part B safety analyses are based on the TE Period for Part B for subjects in the Safety Set for Part B. The TE Period is defined as the time from first dose in this study to 28 days after last dose or completion date of study participation.

The overall long-term safety profile of study drug was planned to be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., serum chemistry, hematology, coagulation, and urinalysis)
- ECGs

- Vital signs including body weight and BMI
- Pulse oximetry
- Spirometry

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

Multiplicity control

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

Interim analyses

Interim analyses may take place at any time during the study at the discretion of the sponsor.

Handling of missing values/censoring/discontinuations

Incomplete/missing data were not planned to be imputed, unless specified otherwise.

CHMP comment

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

Results

Participant flow

Of the 457 subjects who received at least 1 dose of study drug in **Part A**, 411 (89.9%) subjects completed study drug treatment and 412 (90.2%) completed the study (Table 3). A total of 66 (14.4%) subjects who completed Part A rolled over into Part B, which was conducted in certain countries.

Of the 66 subjects who received at least 1 dose of study drug in **Part B**, 8 (12.1%) subjects completed study drug treatment and the study; the majority of subjects (75.8%) discontinued because commercial drug was available (Table 4).

Table 3 Subject Disposition (Part A All Subjects Set)

Disposition Reason	ELX/TEZ/IVA n (%)
All Subjects Set	458
Safety Set	457
Never Dosed	1
Completed treatment	411 (89.9)
Prematurely discontinued treatment	46 (10.1)
Reason for discontinuation of treatment	
AE	2 (0.4)
Subject refused further dosing (not due to AE)	7 (1.5)
Lost to follow-up	5 (1.1)
Commercial drug is available for subject	14 (3.1)
Non-compliance with study drug	2 (0.4)
Physician decision	2 (0.4)
Pregnancy (self or partner)	7 (1.5)
Requires prohibited medication	1 (0.2)
Other	6 (1.3)
Completed study	412 (90.2)
Prematurely discontinued the study	45 (9.8)
Reason for discontinuation from study	
AE	2 (0.4)
Withdrawal of consent (not due to AE)	8 (1.8)
Lost to follow-up	6 (1.3)
Commercial drug is available for subject	13 (2.8)
Other non-compliance	2 (0.4)
Physician decision	2 (0.4)
Other	12 (2.6)
Departed Study 113 to participate in another qualified Vertex study and returned to Study 113	0
Rollover to Part B	66 (14.4)

Source: Table 14.1.1a

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

Notes: All Subjects Set was defined as all subjects who were enrolled (defined as subject having data in the clinical database). Safety Set was defined as all subjects who received at least 1 dose of study drug. Never dosed subjects were selected based on the end of study reason. Percentages are based on the number of subjects in the Safety Set.

Table 4 Subject Disposition (Part B All Subjects Set)

Disposition Reason	ELX/TEZ/IVA n (%)
All Subjects Set	66
Safety Set	66
Never Dosed	0
Completed treatment	8 (12.1)
Prematurely discontinued treatment	58 (87.9)
Reason for discontinuation of treatment	
AE	1 (1.5)
Commercial drug is available for subject	50 (75.8)
Study termination by sponsor	1 (1.5)
Other	6 (9.1)
Completed study	8 (12.1)
Prematurely discontinued the study	58 (87.9)
Reason for discontinuation from study	
AE	1 (1.5)
Commercial drug is available for subject	51 (77.3)
Other	6 (9.1)
Departed Study 113 to participate in another qualified Vertex study and returned to Study 113	0

Source: Table 14.1.1b
AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor
Notes: All Subjects Set was defined as all subjects who were enrolled (defined as subject having data in the clinical database). Safety Set was defined as all subjects who received at least 1 dose of study drug. Never dosed subjects were selected based on the end of study reason. Percentages are based on the number of subjects in the Safety Set.

CHMP comment

Subject dispositions are in line with those of other open-label extension studies of ELX/TEZ/IVA.

Recruitment

Subjects were enrolled at 99 sites in Australia, Canada, Denmark, Germany, Ireland, Israel, Poland, Spain, Switzerland, United Kingdom, and United States.

Study initiation: 09 August 2019 (date first eligible subject signed the informed consent form)
Study completion: 14 December 2022 (date last subject completed the last visit)

Conduct of Study

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

Table 5 Summary of Study 113 Protocol Changes

Protocol Version	Date	Key Changes
1.0	29 May 2019	Original Version
1.1UK	11 June 2019	Original Version in UK
1.2DK	10 September 2019	At the request of the Danish Medicines Agency, language regarding removal of subjects due to commercially available ELX/TEZ/IVA was deleted.
1.3UK	15 April 2021	• Added an optional at-home sweat chloride sample collection for approximately 50 subjects. • Description of interim analysis was removed as requested by MHRA.
1.4US	08 March 2021	Added an optional at-home sweat chloride sample collection for approximately 50 subjects.
1.5AU 1.6CA 1.7ES 1.8PO	08 March 2021	• Extended the Treatment Period by an additional 48 weeks (Part B) to evaluate the safety of ELX/TEZ/IVA beyond 96 weeks of treatment. • Revised the study design to provide the opportunity for subjects who depart this study to enroll in another qualified Vertex study of investigational CFTR modulators, but do not receive the first study drug dose in the Treatment Period of the other study, to return to this study (applies to both Part A and Part B). • Revised the statistical analysis section to reflect the updated study design. • Clarified language regarding height measurement and ophthalmological examination timings for Parts A and B.

ELX: elexacaftor; IVA: ivacaftor; MHRA: The Medicines and Healthcare Products Regulatory Agency; TEZ: tezacaftor

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

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

Important protocol deviations (IPDs) were defined as any protocol deviation that may significantly affect the completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPDs were reported in 3.3% of patients in **Part A**, the majority (3 or 4) were related to informed consent, investigational product or study conduct/procedures (3 or 4 patients each). There were no IPDs in **Part B**.

Baseline data

For **Part A**, demographics are summarised in Table 6 and baseline characteristics are summarised in Table 7.

Table 6 Subject Demographics at Baseline (Part A Safety Set)

Demographic	ELX/TEZ/IVA N = 457
Sex, n (%)	
Male	255 (55.8)
Female	202 (44.2)
Childbearing potential, n (%)	
Yes	197 (97.5)
No	5 (2.5)
Age at baseline (years)	
n	457
Mean (SD)	28.5 (9.8)
Median	28.0
Min, max	13.6, 60.6
Ethnicity, n (%)	
Hispanic or Latino	14 (3.1)
Not Hispanic or Latino	437 (95.6)
Not collected per local regulations	6 (1.3)
Race, n (%)	
White	449 (98.2)
Black or African American	6 (1.3)
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other	1 (0.2)
Not collected per local regulations	5 (1.1)
Geographic Region, n (%)	
North America	252 (55.1)
Europe (including Israel and Australia)	205 (44.9)

Source: Table 14.1.3a
ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part A. Percentages of childbearing women are based on the number of women in the Safety Set. If a subject was reported to have multiple races, then the subject was counted for each race reported.

Table 7 Baseline Characteristics (Part A Safety Set)

Characteristic	ELX/TEZ/IVA N = 457
Weight (kg)	
n	456
Mean (SD)	65.2 (13.4)
Median	64.0
Min, max	36.0, 112.0
Height (cm)	
n	457
Mean (SD)	168.4 (9.8)
Median	168.0
Min, max	140.0, 194.0
BMI (kg/m^2)	
n	456
Mean (SD)	22.86 (3.44)
Median	22.51
Min, max	14.52, 37.89
$ppFEV_1$ category at baseline, n (%)	
<40	4 (0.9)
≥40 to <70	143 (31.3)
≥70 to ≤90	168 (36.8)
>90	80 (17.5)
Missing	62 (13.6)
$ppFEV_1$ at baseline	
n	395
Mean (SD)	75.3 (16.9)
Median	76.3
Min, max	27.6, 128.7

Source: Table 14.1.4a
BMI: body mass index; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part A.

For **Part B**, demographics are summarised in Table 8 and baseline characteristics are summarised in Table 9.

Table 8 Subject Demographics at Baseline (Part B Safety Set)

Demographic	ELX/TEZ/IVA N = 66
Sex, n (%)	
Male	36 (54.5)
Female	30 (45.5)
Childbearing potential, n (%)	
Yes	30 (100.0)
No	0
Age at baseline (years)	
n	66
Mean (SD)	28.4 (9.7)
Median	29.5
Min, max	13.7, 51.8
Ethnicity, n (%)	
Hispanic or Latino	4 (6.1)
Not Hispanic or Latino	62 (93.9)
Not collected per local regulations	0
Race, n (%)	
White	66 (100.0)
Black or African American	0
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other	0
Not collected per local regulations	0
Geographic Region, n (%)	
North America	7 (10.6)
Europe (including Israel and Australia)	59 (89.4)

Source: Table 14.1.3b

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

Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part A. Percentages of childbearing women are based on the number of women in the Safety Set. If a subject was reported to have multiple races, then the subject was counted for each race reported.

Table 9 Baseline Characteristics (Part B Safety Set)

Characteristic	ELX/TEZ/IVA N = 66
Weight (kg)	
n	66
Mean (SD)	64.4 (13.9)
Median	62.0
Min, max	40.0, 103.0
Height (cm)	
n	66
Mean (SD)	169.0 (10.5)
Median	167.0
Min, max	151.0, 194.0
BMI (kg/m^2)	
n	66
Mean (SD)	22.39 (3.43)
Median	22.05
Min, max	14.52, 32.81
$ppFEV_1$ category at baseline, n (%)	
<40	0
≥40 to <70	23 (34.8)
≥70 to ≤90	26 (39.4)
>90	17 (25.8)
$ppFEV_1$ at baseline	
n	66
Mean (SD)	78.5 (19.4)
Median	79.1
Min, max	43.4, 128.7

Source: Table 14.1.4b

BMI: body mass index; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part A.

CHMP comment

In Part A, 457 subjects were enrolled. There was a fairly equal distribution between males and females and geographic region (North America or Europe). Mean age was 28.5 years. Most subjects were white and not Hispanic or Latino. Mean ppFEV1 (SD) at baseline was 75.3 (16.9).

In Part B, 66 subjects were enrolled. Distribution between males and females was still fairly equal. However, 89.4% of the subjects was enrolled in Europe, which is due to not every site offering participation in Part B. Mean age was 28.4 years. All subjects were white and mostly not Hispanic or Latino. Mean ppFEV1 (SD) at baseline was 78.5 (19.4).

Mean SwCl at baseline was not provided in this table but is shown under Efficacy Results. Based on Listing 16.2.4.1a/b provided by the Applicant 81 (17.7%) adolescents were enrolled in Part A and 13 (19.7%) in Part B. The minimum age was 13.7 years.

Number analysed

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

Table 10 Analysis Populations

Analysis Set	Part A	Part B
All Subjects Set	458	66
Safety Set	457	66
Never Dosed	1	0

Source: Table 14.1.1a and Table 14.1.1b
Note: All Subjects Set: all subjects who were enrolled (defined as subject having data in the clinical database); Safety Set: all subjects who received at least 1 dose of study drug; Never Dosed: subjects selected based on the end of study reason.

CHMP comment

The intended sample size of 400 subjects for Part A was reached. Of these 258 subjects, 66 were included in Part B.

Pharmacodynamic results

A summary of SwCl results by genotype is shown in Table 11 and Table 12.

Table 11 Summary of Sweat Chloride Results (mmol/L) and Change from Sweat Chloride Baseline by Genotype at Each Visit through End of Part A

		F/F	F/MF
		ELX/TEZ/IVA	ELX/TEZ/IVA
Visit	Statistics	N = 103	N = 354
Baseline	n	103	353
	Mean (SD)	91.0 (13.9)	102.0 (11.5)
	Median	93.0	103.0
	Min, max	43.0, 119.0	10.0, 141.0
Week 24	n	52	203
	Mean (SD)	40.0 (21.5)	50.1 (19.2)
	Median	35.0	48.5
	Min, max	10.5, 115.5	10.5, 132.0
Change at Week 24	n	52	203
	Mean (SD)	-50.9 (17.8)	-52.6 (18.8)
	Median	-54.0	-53.0
	Min, max	-82.0, 5.5	-93.5, 25.0
Week 96	n	88	297
	Mean (SD)	39.5 (17.7)	51.8 (20.0)
	Median	40.0	48.5
	Min, max	11.0, 99.0	10.0, 107.5
Change at Week 96	n	88	296
	Mean (SD)	-52.3 (17.4)	-50.6 (20.2)
	Median	-53.5	-52.0
	Min, max	-91.5, 5.0	-100.5, 14.0

- Baseline is defined as the most recent non-missing sweat chloride (scheduled or unscheduled) collected before the first dose of VX-659 in VX17-659-102 or VX17-659-103 studies.
- Summary of Week 96 is based on all sweat chloride data assessed beyond Day 421.

Table 12 Summary of Sweat Chloride Results (mmol/L) and Change from Sweat Chloride Baseline by Genotype at Each Visit of Part B

		F/F	F/MF
		ELX/TEZ/IVA	ELX/TEZ/IVA
Visit	Statistics	N = 21	N = 45
Baseline	n	21	45
	Mean (SD)	90.2 (10.0)	102.6 (7.6)
	Median	88.5	103.5
	Min, max	64.0, 105.5	81.0, 118.5
Part B Week 24	n	18	42
	Mean (SD)	36.9 (18.5)	57.1 (19.3)
	Median	31.5	56.3
	Min, max	13.0, 79.0	18.0, 107.5
Change at Part B Week 24	n	18	42
	Mean (SD)	-53.4 (18.5)	-45.6 (17.6)
	Median	-57.3	-48.5
	Min, max	-84.0, -14.0	-76.5, -2.0
Part B Week 48	n	2	11
	Mean (SD)	29.5 (12.0)	55.7 (13.0)
	Median	29.5	52.0
	Min, max	21.0, 38.0	37.0, 78.5
Change at Part B Week 48	n	2	11
	Mean (SD)	-66.8 (3.9)	-48.7 (15.6)
	Median	-66.8	-49.0
	Min, max	-69.5, -64.0	-70.5, -25.0

– Baseline of sweat chloride is defined as the most recent non-missing sweat chloride (scheduled or unscheduled) collected before the first dose of VX-659 in VX17-659-102 or VX17-659-103 studies.

CHMP comment

The median change in SwCl in Part A at week 24 was -54.0 mmol/L in F/F patients and -53.0 mmol/L in F/MF patients. The median change in Part B at week 24 was -57.3 and -48.5, respectively. For both genotypes, SwCl levels decreased during the first 24 weeks of Study 113 and then remained relatively stable. The decrease in SwCl was more or less in line with (or even slightly better compared to) observed values in previous studies.

Efficacy results

N/A

Safety results

Safety population

The safety set consisted of all subjects who received at least 1 dose of study drug. Safety data is provided per study part.

Exposure

The **Part A** Safety Set included 457 subjects who had a mean exposure of 91.9 weeks, representing 874.9 patient-years of exposure (Table 13).

Table 13 Summary of Exposure (Part A Safety Set)

	ELX/TEZ/IVA N = 457
Total exposure (patient weeks)	41993.0
Total exposure (patient years)	874.9
Exposure duration (weeks)	
n	457
Mean (SD)	91.9 (15.5)
Median	96.0
Min, max	1.1, 101.3
Exposure duration by interval, n (%)	
≤24 weeks	9 (2.0)
>24 to ≤48 weeks	11 (2.4)
>48 to ≤72 weeks	13 (2.8)
>72 to ≤96 weeks	247 (54.0)
>96 weeks	177 (38.7)

Source: Table 14.1.7a
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 of study drug– first dose date of study drug + 1)/7, regardless of study drug interruption, excluding the time between the last dose before the discontinuation from Part A and the first dose after re-enrollment in Part A. Duration of study drug exposure (years) = (last dose date of study drug - first dose date of study drug + 1)/336, regardless of study drug interruption; 1 year = 48 weeks = 336 days.

The **Part B** Safety Set included 66 subjects who had a mean exposure of 24.2 weeks, representing 33.2 patient-years of exposure (Table 14).

Table 14 Summary of Exposure (Part B Safety Set)

	ELX/TEZ/IVA N = 66
Total exposure (patient weeks)	1595.9
Total exposure (patient years)	33.2
Exposure duration (weeks)	
n	66
Mean (SD)	24.2 (13.3)
Median	24.0
Min, max	0.4, 53.0
Exposure duration by interval, n (%)	
≤24 weeks	38 (57.6)
>24 to ≤48 weeks	25 (37.9)
>48 to ≤72 weeks	3 (4.5)
>72 to ≤96 weeks	0
>96 weeks	0

Source: Table 14.1.7b
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 of study drug– first dose date of study drug + 1)/7, regardless of study drug interruption, excluding the time between the last dose before the discontinuation from Part B and the first dose after re-enrollment in Part B. Duration of study drug exposure (years) = (last dose date of study drug - first dose date of study drug + 1)/336, regardless of study drug interruption; 1 year = 48 weeks = 336 days.

Adverse events

In **Part A**, 435 (95.2%) subjects had at least 1 AE and 75 (16.4%) had at least 1 serious AE (SAE). See Table 15. The majority of subjects had AEs that were mild or moderate in severity. Overall, 44 (9.6%) subjects had at least 1 severe AE, 3 (0.7%) subjects had a life-threatening AE, and there were no deaths. Fourteen (3.1%) subjects interrupted ELX/TEZ/IVA due to AEs, and 2 (0.4%) subjects discontinued ELX/TEZ/IVA due to AEs.

Table 15 Overview of AEs (Part A Safety Set)

	ELX/TEZ/IVA N = 457	
	n (%)	Events/100PY
Number of AEs (Total)	3904	--
Total duration of safety analysis period in 100 PY	--	8.81
Subjects with any AEs	435 (95.2)	443.06
Subjects with AEs by strongest relationship		
Not related	146 (31.9)	--
Unlikely related	152 (33.3)	--
Possibly related	124 (27.1)	--
Related	13 (2.8)	--
Subjects with AEs by maximum severity		
Mild	168 (36.8)	--
Moderate	220 (48.1)	--
Severe	44 (9.6)	--
Life-threatening	3 (0.7)	--
Missing	0	--
Subjects with AEs leading to study drug discontinuation	2 (0.4)	0.57
Subjects with AEs leading to study drug interruption	14 (3.1)	2.95
Subjects with Grade 3/4 AEs	47 (10.3)	11.12
Subjects with related AEs	137 (30.0)	42.10
Subjects with SAEs	75 (16.4)	13.96
Subjects with related SAEs	0	0
Subjects with AEs leading to death	0	0

Source: Table 14.3.1.1a

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

Notes: MedDRA Version 25.0 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. An AE with relationship missing was counted as related.

In **Part B**, 50 (75.8%) subjects had at least 1 AE and 4 (6.1%) had at least 1 SAE (Table 16). The majority of AEs were mild or moderate in severity. Three (4.5%) subjects had at least 1 severe AE, no subjects had a life-threatening AE, and there were no deaths. No subjects interrupted ELX/TEZ/IVA due to AEs, and 1 (1.5%) subject discontinued ELX/TEZ/IVA due to AEs.

Table 16 Overview of AEs (Part B Safety Set)

	ELX/TEZ/IVA N = 66	
	n (%)	**Events/100PY**
Number of AEs (Total)	169	--
Total duration of safety analysis period in 100 PY	--	0.34
Subjects with any AEs	50 (75.8)	504.16
Subjects with AEs by strongest relationship		
Not related	28 (42.4)	--
Unlikely related	16 (24.2)	--
Possibly related	5 (7.6)	--
Related	1 (1.5)	--
Subjects with AEs by maximum severity		
Mild	30 (45.5)	--
Moderate	17 (25.8)	--
Severe	3 (4.5)	--
Life-threatening	0	--
Missing	0	--
Subjects with AEs leading to study drug discontinuation	1 (1.5)	5.97
Subjects with AEs leading to study drug interruption	0	0
Subjects with Grade 3/4 AEs	3 (4.5)	20.88
Subjects with related AEs	6 (9.1)	35.80
Subjects with SAEs	4 (6.1)	20.88
Subjects with related SAEs	0	0
Subjects with AEs leading to death	0	0

Source: Table 14.3.1.1b

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

Notes: MedDRA Version 25.1 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted. An AE with relationship missing was counted as related.

CHMP comment

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

More importantly, frequencies and events/100PY are in line with (or even lower compared to) other long-term safety studies of ELX/TEZ/IVA.

Common Adverse Events

Table 17 shows all AEs that occurred in at least 10% of subjects in Study 113 **Part A**, summarised by PT. Most common AEs were infective pulmonary exacerbation of CF, cough, and headache.

Table 17 AEs With an Incidence ≥10% by PT (Part A Safety Set)

	ELX/TEZ/IVA N = 457	
PT	**n (%)**	**Events/100PY**
Subjects with any AEs	435 (95.2)	443.06
Infective pulmonary exacerbation of cystic fibrosis	118 (25.8)	30.76
Cough	114 (24.9)	19.29
Headache	92 (20.1)	16.46
Upper respiratory tract infection	71 (15.5)	12.14
Sputum increased	67 (14.7)	10.67
Pyrexia	63 (13.8)	11.80
Nasopharyngitis	61 (13.3)	10.33
Oropharyngeal pain	61 (13.3)	10.10
Nasal congestion	52 (11.4)	8.17
Fatigue	46 (10.1)	6.81
Viral upper respiratory tract infection	46 (10.1)	6.36

Source: Table 14.3.1.3a

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

Notes: MedDRA Version 25.0 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency by PT.

AEs that occurred in at least 10% of subjects in Study 113 **Part B** are shown in Table 18.

Table 18 AEs With an Incidence ≥10% by PT (Part B Safety Set)

	ELX/TEZ/IVA N = 66	
PT	**n (%)**	**Events/100PY**
Subjects with any AEs	50 (75.8)	504.16
COVID-19	18 (27.3)	53.70
Infective pulmonary exacerbation of cystic fibrosis	12 (18.2)	47.73
Upper respiratory tract infection	10 (15.2)	29.83

Source: Table 14.3.1.3b

AE: adverse event; COVID-19: coronavirus disease; ELX: elexacaftor; IVA: ivacaftor; PT: Preferred Term; PY: patient-years; TEZ: tezacaftor

Notes: MedDRA Version 25.1 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency by PT.

CHMP comment

Overall, AEs were consistent with common manifestations or CF disease, common illnesses in CF subjects 12 years of age and older, or the known safety profile of ELX/TEZ/IVA. Frequencies are comparable to those in other long-term safety studies.

Severity of Adverse Events

In **Part A**, the majority of subjects had AEs that were mild (36.8%) or moderate (48.1%) in severity (Table 15). Forty-four (9.6%) subjects had severe AEs, and 3 (0.7%) subjects had life-threatening AEs. Life-threatening AEs were adenocarcinoma of colon and abdominal abscess (1 subject), haemoptysis (1 subject), and ovarian cyst ruptured (1 subject). All events were considered not related or unlikely related to ELX/TEZ/IVA by the investigator.

In **Part B**, there was only three severe AEs (4.5%), all others were either mild (45.5%) or moderate (25.8%).

Relationship of Adverse Events

In **Part A**, 13 (2.8%) subjects had AEs assessed by the investigator as related, and 124 (27.1%) subjects had AEs assessed by the investigator as possibly related. AEs designated as related or possibly related that occurred in ≥3% of subjects were alanine aminotransferase (ALT) increased (4.8%), aspartate aminotransferase (AST) increased (4.4%), and blood creatine phosphokinase increased (3.1%).

In **Part B**, 1 (1.5%) subject had an AE assessed by the investigator as related, and 5 (7.6%) subjects had AEs assessed by the investigator as possibly related. AEs designated as related or possibly related that occurred in ≥3% of subjects were alanine aminotransferase (ALT) increased (4.5%) and aspartate aminotransferase (AST) increased (4.5%).

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

There were no AEs leading to death in both parts of the study.

In **Part A**, 75 (16.4%) subjects had at least 1 SAE. SAEs occurring in ≥2 subjects are presented in Table 19. No SAEs were assessed as related to study drug.

Table 19 SAEs Occurring in ≥2 Subjects by PT (Part A Safety Set)

	ELX/TEZ/IVA N = 457	
PT	**n (%)**	**Events/100PY**
Subjects with any SAEs	75 (16.4)	13.96
Infective pulmonary exacerbation of cystic fibrosis	31 (6.8)	5.56
Pneumonia	7 (1.5)	0.79
Distal intestinal obstructive syndrome	3 (0.7)	0.45
Hemoptysis	3 (0.7)	0.34
COVID-19	2 (0.4)	0.23
Influenza	2 (0.4)	0.23
Pancreatitis acute	2 (0.4)	0.23
Small intestinal obstruction	2 (0.4)	0.23
Pyrexia	2 (0.4)	0.23
Acute kidney injury	2 (0.4)	0.23
Nephrolithiasis	2 (0.4)	0.34
Cystic fibrosis-related diabetes	2 (0.4)	0.23

Source: Table 14.3.2.1a

COVID-19: coronavirus disease; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; PY: patient-years; SAE: serious adverse event; TEZ: tezacaftor

Notes: MedDRA Version 25.0 was used. Events/100PY: number of events per 100 PY (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100 PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percent of subjects, a subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency by PT.

In **Part B**, 4 (6.1%) subjects had SAEs, which were stoma site discharge (mild; unlikely related), distal intestinal obstruction syndrome (severe; unlikely related), concurrent infections (PEx of CF, human rhinovirus, influenza A and SARS-CoV-2) (all severe; unlikely related), and ligament rupture (mild, not related).

CHMP comment

Overall, related AEs and SAEs were consistent with common CF manifestations and complications, as well as with the known safety profile for ELX/TEZ/IVA.

Study Drug Discontinuation

In **Part A**, 2 (0.4%) subjects had AEs that led to treatment discontinuation. One event was acute kidney injury and concurrent AEs of bilirubin conjugated increased, blood alkaline phosphatase (ALP) increased, and blood bilirubin increased (all moderate; unlikely related; not resolved at time of reporting). The other event was abdominal distension (mild; possibly related; resolved).

In **Part B**, 1 (1.5%) subject had AEs of ALT and AST increased (moderate; related; resolved).

Adverse Events That Led to Interruption of Study Drug

In **Part A**, 14 (3.1%) subjects had AEs that led to study drug interruption. AEs leading to treatment interruption occurring in at least 2 subjects were AST increased (4 subjects), blood creatine phosphokinase increased (4 subjects), and ALT increased (2 subjects).

No subject in **Part B** interrupted study drug due to AEs.

CHMP comment

The number of subjects who had AEs leading to drug interruption is comparable to what was seen during the initial marketing authorisation and other long-term safety studies of ELX/TEZ/IVA.

Adverse Events of Special Interest

Elevated Transaminase Events

In **Part A**, 43 (9.4%) subjects had at least 1 elevated transaminase event. ALT increased occurred in 39 (8.5%) subjects, while AST increased occurred in 31 (6.8%) subjects. The majority of events were mild (7.0%) or moderate (2.0%) in severity. None of the events were serious or led to treatment discontinuation. Five (1.1%) subjects had elevated transaminase events that led to treatment interruption.

In **Part B**, 3 (4.5%) subjects had at least 1 elevated transaminase event. Both ALT increased and AST increased occurred in 3 (4.5%) subjects. One event was mild, while the other two were moderate in severity. None of the events were serious. One (1.5%) subject had elevated transaminase events that led to treatment discontinuation.

Rash Events

In **Part A**, 48 (10.5%) subjects had a rash event. The majority of events were mild or moderate in severity, and none were serious. No subject had a rash event that led to treatment discontinuation, and 2 (0.4%) subjects had a rash event that led to treatment interruption.

By sex, 23/202 (11.4%) female subjects and 25/255 (9.8%) male subjects had rash events. In female subjects, 11/67 (16.4%) subjects who used hormonal therapy and 12/135 (8.9%) subjects not using hormonal therapy had rash events.

In **Part B**, 2 (3.0%) subjects had a rash event. These events were mild or moderate in severity, and none were serious. No subject had a rash event that led to treatment discontinuation or interruption.

By sex, 2/30 (6.7%) female subjects and no male subjects had rash events. In female subjects, 1/8 (12.5%) subjects who used hormonal therapy and 1/22 (4.5%) subjects not using hormonal therapy had rash events.

CHMP comment

Elevated transaminases and rash are known AEs of ELX/TEZ/IVA. During the initial marketing application, a higher incidence of rash was seen in female subjects taking hormonal therapy compared with those not taking hormonal therapy in the ELX/TEZ/IVA arm. The same trend is seen in this study. Nonetheless, there are no new insights in the AESIs of elevated transaminases and rash.

Clinical Laboratory Evaluation

Chemistry

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

Haematology

There were no trends observed in haematology parameters in **Part A** or **Part B**. Overall, AEs related to haematology were infrequent, not serious and did not lead to treatment discontinuation. In Part A, 1 (0.2%) subject interrupted study drug due to AEs of leukopenia and neutropenia.

Coagulation

There were no trends observed in coagulation parameters in **Part A** or **Part B**. Overall, AEs related to coagulation parameters were infrequent, not serious and did not lead to treatment interruption or discontinuation.

Urinalysis

There were no trends in urinalysis results in **Part A** or **Part B**. AEs related to urinalysis were infrequent, not serious and did not lead to treatment discontinuation or interruption.

Vital signs

Part A: The mean (SD) systolic and diastolic blood pressure increased from baseline through Week 96 by 3.6 (12.5) and 2.7 (9.9) mm HG, respectively. Mean blood pressures were variable over time.

Part B: By Week 48, the mean change in systolic blood pressure ranged from -1.8 (10.2) to 4.4 (10.9) mm Hg, while the mean increase in diastolic blood pressure ranged from 1.6 (7.2) to 4.0 (7.4) mm Hg.

Overall, AEs related to vital signs parameters were infrequent in both parts, not serious and did not lead to treatment interruption or discontinuation.

Pulse Oximetry

There were no trends in pulse oximetry in **Part A** or **Part B**.

ECG

There were no trends observed in ECG parameters in **Part A** or **Part B**. AEs related to ECG findings or relevant cardiac disorders were infrequent and did not lead to treatment discontinuation or interruption.

Ophthalmologic Examinations

In **Part A**, 2 (0.4%) subjects had an AE of cataract cortical, and 1 (0.2%) subject had an AE of cataract. All AEs were mild, nonserious and did not lead to change in study drug dosing.

There were no AEs related to ophthalmologic examination findings in **Part B**.

Spirometry

There was no trend of worsening in spirometry results in **Part A** or **Part B**.

CHMP comment

Clinical laboratory findings are in line with those observed in previous long-term safety studies.

2.3.3. Discussion on clinical aspects

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

submitted the results of a stand-alone study, Study VX18-445-113 ("Study 113"), as per requirement of Article 46 of the "Paediatric Regulation" (EC) 1901/2006.

Study 113 is a Phase 3, multicenter, open-label study (OLS) in CF subjects 12 years of age and older, homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and a minimal function mutation (F/MF genotypes), who transferred from Study VX17-659-105 (Study 659-105). The study consisted of two parts: Part A (96 weeks Treatment Period) and, in certain countries, Part B (48 weeks Treatment Period), followed by a 4-week Safety Follow-up Period. During the Treatment Period, patients received standard ELX/TEZ/IVA treatment as described in the SmPC. Inclusion and exclusion criteria are considered acceptable.

The primary objective was safety and tolerability of long-term treatment with ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, pulse oximetry, and spirometry. This endpoint is appropriate for an open-label extension study. There were no efficacy endpoints analysed, but SwCl levels were assessed as a pharmacodynamic endpoint.

A total of 457 subjects were enrolled in Part A (400 subjects were planned), of these, 66 subjects rolled over to Part B. Only 8 subjects (12.1%) completed Part B, which was mainly due to commercial drug being available. As such, results for Part A are considered most important for this procedure. The mean age in Part A was 28.5 years and in Part B was 28.4 years.

SwCl levels decreased during the first 24 weeks of Study 113 for both genotypes and then remained relatively stable. Results of this pharmacodynamic endpoint were in line with previous observed results in F/F and F/MF patients.

Adverse events were generally mild or moderate in severity. In Part A, 3 subjects had 4 life-threatening AEs, but these were considered not related or unlikely related to study drug. Most common AEs were infective PEx of CF, cough, and headache, all of which occurred in more than 20% of the subjects. AEs leading to study drug interruption or discontinuation were rare and mainly liver-related events. There were no new insights in the AESIs of elevated transaminases and rash. In general, AEs were consistent with common manifestations and complications of CF disease in subjects 12 years of age and older, or the known safety profile of ELX/TEZ/IVA.

Conclusion

No new safety signals were observed in Study 113. Results for the pharmacodynamic endpoint SwCl were in line with previous obtained results in the F/F and F/MF patient populations aged 12 years and older. As such, no update of the SmPC is requested, which is endorsed.

3. Rapporteur's overall conclusion and recommendation

The benefit-risk evaluation of Kaftrio remains positive. No new safety signals were observed for CF patients aged 12 years and older with F/F and F/MF genotypes treated with ELX/TEZ/IVA in Study 113.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled: