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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/P46/014

Note

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

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1. Introduction

On 1 June 2023, the MAH submitted a completed paediatric study VX19-445-115 for Kaftrio (elexacaftor/tezacaftor/ivacaftor) 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 Applicant submitted the results of study VX19-445-115. The MAH stated that study VX19-445-115, title Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects is stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study VX19-445-115, the following tablets were used:

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

• 150-mg IVA tablet

All these tablets are authorised for this population and age group. The applied posology aligns with the dose approved for patients aged ≥ 12 years.

- Morning dose two tablets of elexacaftor/tezacaftor /ivacaftor 100/50/75 mg
- Evening dose : one tablet of 150 mg ivacaftor

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report(s) for: study number VX19-445-115. The study included patients who had previously participated in study VX18-445-109.

Assessor's comment

Background information
Study VX18-445-109 has been under review as EMEA/H/C/005269/P46/007. Study VX 18-445-109 was a phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for *F508del*, aged 12 years or older.

The study is an open label study and was started on 3 Oct 2019 and completed on July 24, 2020. The study included a total of 176 homozygotic F/F patients with an FEV1 between 40-90% of predicted and no protocol defined laboratory values indicative of abnormal liver or renal function. Following TEZ/IVA run-in period of 4 weeks, participants received TEZ 100 mg qd/IVA 150 mg q12h (Symkevi) or ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (Kaftrio) in the treatment period for 24 weeks.

Study VX18-445-109 included a total of 176 F/F patients. A total of 172 patients completed the study period. One subject was randomised but not treated as the subject experienced an CF exacerbation before the start of the study. The other 3 patients prematurely left the trial because of an adverse event.

The Study met its primary endpoint with an improvement in CFQ-R RD score of 15.9 points through Week 24 (95% CI: 11.7, 20.1; p<0.0001).

Safety

Adverse events were generally mild or moderate in severity and there were no life-threatening AEs or AEs leading to death.

SAEs were reported with a frequency of 5.7% in the ELX/TEZ/IVA group.

Adverse events of special interest (AESI) were transaminase elevations and rash.

A total of 6.9% showed at least 1 elevated transaminase event, while treated with ELX/TEZ/IVA; four patients experienced an event with ALT or AST >5 ULN and one an event of ALT or AST >8. None of the subjects experienced an event of (ALT >3 × ULN or AST >3 × ULN) and TBILI >2 × ULN.
Two (2.3%) subjects in the ELX/TEZ/IVA group had elevated transaminase events that led to study drug interruption; 1 of these events was serious.

Rash was reported in 12.6% of patients in the ELX/TEZ/IVA group and did not lead to study discontinuation.

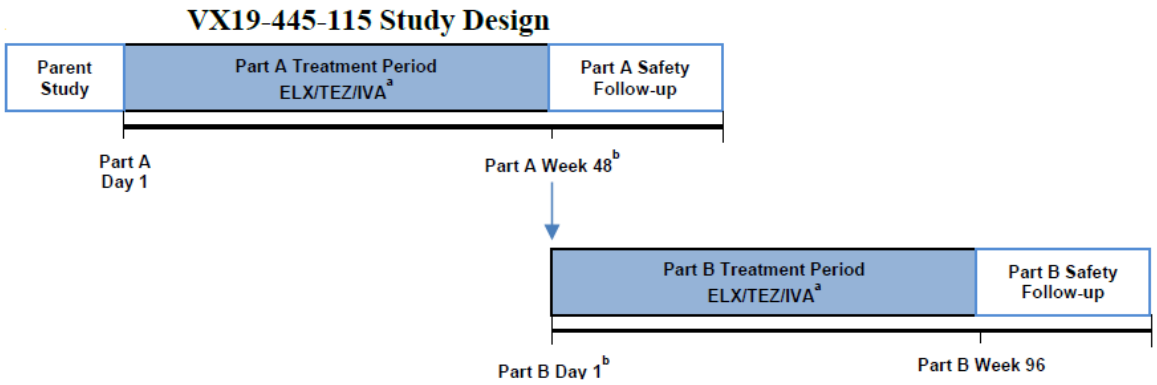
Clinical study number and title

Study VX19-445-115 is a Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects (F508/F508).

Description

Study VX19-445-115 was a Phase 3b, 2-part, multicentre, open-label study for subjects aged 12 years or older who completed a parent study (Study VX18-445-109) and met eligibility criteria.

The total planned 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 (48 weeks in Part A and 96 weeks in Part B [in certain countries]) and a 4-week Safety Follow-up Period.



ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Figure is not drawn to scale.

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

[b] Subjects whose Part B Day 1 was on the same day or within 1 calendar day of the Part A Week 48 Visit did NOT have to repeat any Part B Day 1 assessments that were specified to be performed at the Part A Week 48 Visit. Subjects whose Part B Day 1 was more than 1 calendar day after Part A Week 48 Visit had to complete all assessments specified for the Part A Week 48 AND Part B Day 1 Visits.

Methods

Study participants

The patients who were eligible for study VX19-445-115 had completed study VX18-445-109. The key additional in-and exclusion criteria were:

Inclusion criteria	Exclusion criteria
Did not withdraw consent from a parent study and (if continuing to Part B of this study) did not withdraw. consent in Part A • For each part of the study, met the following criteria: • for subjects entering Part A of this study: ☐ Completed study drug treatment in a parent study, or Had study drug interruptions(s) in a parent study, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of a parent study. for subjects continuing on to Part B of this study: ☐ Completed study drug treatment in Part A, or ☐ Had study drug interruptions(s) in Part A, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of Part A. • for subjects being considered for resumption of participation in this study after enrolling in another qualified Vertex study: ☐ Completed the ETT visit in another qualified Vertex study before or on the same day as the Returning Visit in this study. If more than 30 days had elapsed since the ETT visit in the other qualified Vertex study, approval of the medical monitor was required, and ☐ Did not depart this study more than once to participate in another qualified Vertex study.•	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 a parent study that would pose an additional risk to the subject Current participation in an investigational drug trial other than a parent study or the current study. Participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) and screening for another Vertex study was permitted. • For subjects being considered for resumption of participation in this study after enrolling in another qualified Vertex study, the following exclusion criteria also applied: ☐ Subject received the first dose of study drug in the Treatment Period of another qualified Vertex study, or ☐ Subject had access to commercially available or managed-access-program-supplied ELX/TEZ/IVA.

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.

Objective

The primary objective was to evaluate safety and tolerability of ELX/TEZ/IVA in subjects with CF who are homozygous for *F508del*.

Outcomes/endpoints

The primary endpoints were the safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry.

Sample size

Up to approximately 158 subjects were expected to enroll in this open-label extension study.

Randomisation and blinding

Not applicable. The study had an open-label design.

Statistical Methods

The safety analysis was to be conducted for subjects who had received at least 1 dose of study drug in this open-label study. The safety analysis was to be descriptive only.

Conduct of the trial

GCP

The study was to be conducted following GCP.

Amendments

The original protocol was dated 12 September 2019. Country specific amendments were prepared for 2 countries (AU and BE) to extent the treatment period with part B of the study; following amendment 2.1., patients were allowed resume participation if they had departed this study to be enrolled in another Vertex study.

Table 1: Summary of Study 115 Protocol Changes

Protocol Version	Date	Key Changes
1.0	12 September 2019	Original Version
2.0 AU and BE	04 January 2021	Updated to extend treatment period.
2.1 AU and BE	19 March 2021	Updated to allow subjects who departed this study to enroll in another qualified Vertex study to return to this study if they did not receive study drug in the Treatment Period of the other qualified Vertex study.
2.2 AU and BE	21 December 2021	Current version, extended the Part B study period by an additional 48 weeks.

AU: Australia; BE: Belgium

Covid

The study was conducted during the COVID 19 pandemic. During the study Safety measures were implemented to continue participation in this study while ensuring their safety by minimizing the risk to coronavirus disease (COVID-19) exposure through travel. These measures were enabled based on country and local regulations and site-level considerations (e.g., site closure due to COVID-19).

Results

Participant flow

The first patient first visit was on 24 April 2020 and on 21 Dec 2022 the last subject completed the last visit.

Part A

Of the 172 subjects who received at least 1 dose of study drug in Part A, 157 (91.3%) subjects completed study drug treatment and 159 (92.4%) completed the study.

- A total of 15 (8.7%) subjects discontinued treatment because of AE (n=3), refused further dosing (not AE) n=4), commercial availability (n=2), pregnancy (self or partner) (n=5) or required prohibited medication (n=1).
- A total of 13 (7.6%) subjects discontinued the study because of AE (n=2), withdrawal of consent (n=4), commercial availability (n=2) and other (n=5).

Part B

A total of 50 subjects who completed Part A rolled over into Part B. None of the subjects completed treatment or the study.

Most subjects (46 [92.0%] subjects) discontinued the treatment and study due to commercial drug availability. The other 4 patients discontinued to transition to a managed access program. None of the participants were enrolled in another qualified Vertex study and resumed participation in this study.

Demographics and disease characteristics

Part A

A total of 172 patients were included. The mean (SD) age at parent study baseline was 27.9 (11.4) years, and 50.6% of the subjects were female. Most subjects (98.8%) were White.

The mean (SD) ppFEV1 at screening was 63.3 (15.9)%. A total of 51 (29.7%) subjects was aged < 18 years.

The most common concomitant medications were those typically used for the management of CF.

Part B:

A total of 50 patients were included. The mean (SD) age at parent study baseline was 25.6 (12.0) years, and 52% of the subjects were female. All subjects were White.

The mean (SD) ppFEV1 at screening was 58.9 (15.6) %. A total of 18 (36%) was aged < 18 years.

Efficacy results

Not applicable.

Number analysed

Part A: A total of 172 subjects received at least 1 dose of study drug in Part A.

Part B: A total of 50 subjects who completed Part A rolled over into Part B and received as least one study dose.

Safety results

Exposure

Part A: The median exposure in part A is 48.0 weeks (min 4.1 week, max 50.6 weeks). Most patients (> 70%) had an exposure of at least 36 weeks.

Part B: None of the 50 included patients completed treatment or the study (the maximum exposure was 86 weeks). The Safety Set for Part B included 50 subjects who had a mean exposure of 62.0 weeks, representing 3101.3 patient-weeks of exposure The maximum exposure was 86 weeks.

General description adverse events

Part A

In Part A, 160 (93.0%) subjects had at least 1 AE and 26 (15.1%) subjects had at least 1 serious adverse event (SAE).

Most subjects had AEs that were mild (43.0%) or moderate (46.3%) in severity. Ten (5.8%) subjects had severe AEs, including 4 drug related SAE. One (0.6%) subject had a non-drug related life-threatening AE, and there were no deaths. (Table 2).

Twelve (7.0%) subjects interrupted ELX/TEZ/IVA due to AEs, including 7 subjects with a treatment interruption due to a drug related event interruption. A total of 3 (1.7%) subjects discontinued ELX/TEZ/IVA due to a drug related adverse event.

Part B

In part B, all subjects had at least 1 AE and 8 (16.0%) had at least 1 SAE. Most subjects had AEs that were mild (32%) or moderate (56%) in severity. Six (12.0%) subjects had severe AEs; there were no life-threatening AEs and no deaths. No subjects interrupted ELX/TEZ/IVA due to AEs and there were no treatment discontinuations due to AEs (Table 3).

Table 2: Overview of AEs (Part A, Safety Set)

Category	ELX/TEZ/IVA N = 172 n (%)	Events/100PY
Number of AEs (Total)	1062	--
Total duration of treatment-emergent period in 100 PY	--	1.66
Subjects with any AEs	160 (93.0)	638.61
Subjects with AEs by strongest relationship		
Adverse events with being at least drug related	69 (40.1%)	--
Subjects with AEs by maximum severity		
Mild	74 (43.0)	--
Moderate	75 (43.6)	--
Severe	10 (5.8)	--
Life-threatening	1 (0.6)	--
Missing	0	--
Subjects with AEs leading to study drug discontinuation	3 (1.7)	5.41
Subjects with AEs leading to study drug interruption	12 (7.0)	19.24
Subjects with related SAEs	4 (2.3)	6.01
Subjects with Grade 3/4 AEs	11 (6.4)	15.03
Subjects with related AEs	69 (40.1)	132.29
Subjects with SAEs	26 (15.1)	27.06
Subjects with AEs leading to death	0	0

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 patient years (336 days=48 weeks per year) = number of events/total duration of treatment-emergent period for Part A in 100PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage 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. Subjects with Grade 3/4 AEs included the 'Severe' and 'Life Threatening' categories. If subjects only had one event which had missing severity, then the subject was summarized in the "Missing" category. An AE with relationship missing was counted as Related. "--" indicates that no data was available.

Table 3: Overview of AEs (Part B, Safety Set)

Category	ELX/TEZ/IVA N = 50 n (%)
Number of AEs (Total)	321
Subjects with any AEs	50 (100.0)
Subjects with AEs by strongest relationship	
Not related	23 (46.0)
Unlikely related	20 (40.0)
Possibly related	6 (12.0)
Related	1 (2.0)
Subjects with AEs by maximum severity	
Mild	16 (32.0)
Moderate	28 (56.0)
Severe	6 (12.0)
Life-threatening	0
Missing	0
Subjects with AEs leading to study drug discontinuation	0
Subjects with AEs leading to study drug interruption	0
Subjects with related SAEs	0
Subjects with Grade 3/4 AEs	6 (12.0)
Subjects with related AEs	7 (14.0)
Subjects with SAEs	8 (16.0)
Subjects with AEs leading to death	0

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

Adverse event

Part A

Adverse events

Adverse events that occurred with an incidence ≥10% were headache (24.4%), nasopharyngitis (16.3%), vaccination complication (14.0%), cough (13.4%), infective PEx of CF (11.6%) and sputum increased (11.0%).

One subject had a life-threatening event of an AE of myocardial infarction considered not to be related to study medication.

Related adverse events

Part A: a total of 69 subjects (40.1%) had AEs as assessed as being at least possibly related to medication. These AEs occurred most frequently in the SOC Investigations (n=22 (12.8%) and referred to lab values associated with hepatocellular injury (e.g. AST increased, ALT increased). Other related AEs frequently occurred in the SOC Respiratory, thoracic, and mediastinal disorders (n=21 (12.2%), Gastrointestinal disorders (n=15 (8.7%) and Nervous system disorders (n=13 (7.6%).

The reported drug-related AE with reported frequency > 5% were headache (n=10 (5.8%), sputum increased (n=10 (5.8%), AST increased (n=9 (5.2%) and blood bilirubin increased (n=9 (5.2%).

Part B

Adverse events

Adverse events that occurred with an incidence ≥ 10% were Infective PEx of CF (n=24 (48.0%)), COVID-19 (n=17 (34.0 %)), Nasopharyngitis (n=16 (32.0%)), Upper respiratory tract infection (n=11 (22.0 %)), Headache (n=10 (20.0 %)), Pyrexia (n=8 (16.0%)), Immunization reaction (n=7 (14.0 %)), Productive cough (n=7 (14.0 %)), Cough (n=5 (10.0 %)), Oropharyngeal pain (n=5 (10.0 %)), Sputum increased (n=5 (10.0%)). (Table 4)

Table 4: AEs With an Incidence ≥10% by PT (Part B, Safety Set) ELX/TEZ/IVA

	ELX/TEZ/IVA N = 50
PT	**n (%)**
Subjects with any AEs	50 (100.0)
Infective PEx of CF	24 (48.0)
COVID-19	17 (34.0)
Nasopharyngitis	16 (32.0)
Upper respiratory tract infection	11 (22.0)
Headache	10 (20.0)
Pyrexia	8 (16.0)
Immunisation reaction	7 (14.0)
Productive cough	7 (14.0)
Cough	5 (10.0)
Oropharyngeal pain	5 (10.0)
Sputum increased	5 (10.0)

AE: adverse event; CF: cystic fibrosis; COVID-19: coronavirus disease; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor Notes: MedDRA Version 25.1 was used. When summarizing number and percentage 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.

Related adverse events.

A total of 7 (14%) subjects had an AE considered to be related to medication. A total of 3 subjects experienced a drug related AE in the SOC investigations (ALT increased, CK increased, Systolic Blood pressure increased, while only one subject experienced a drug related AE in the SOC infections and infestations (pulmonary exacerbation). (Table 5).

Table 5: Related TEAEs by System Organ Class and Preferred Term - Part B Safety Set

System Organ Class Preferred Term	ELX/TEZ/IVA N = 50 n (%)
Subjects with any related TEAEs	7 (14.0)
Investigations	3 (6.0)
Alanine aminotransferase increased	1 (2.0)
Blood creatine phosphokinase increased	1 (2.0)
Blood pressure systolic increased	1 (2.0)
Infections and infestations	1 (2.0)
Infective pulmonary exacerbation of cystic fibrosis	1 (2.0)
Metabolism and nutrition disorders	1 (2.0)
Hypercholesterolaemia	1 (2.0)
Nervous system disorders	1 (2.0)
Headache	1 (2.0)
Psychiatric disorders	1 (2.0)
Depression	1 (2.0)
Respiratory, thoracic and mediastinal disorders	1 (2.0)
Pulmonary mass	1 (2.0)
Vascular disorders	1 (2.0)
Hypertension	1 (2.0)

Serious adverse events

Part A

Twenty-six (15.1%) subjects had at least 1 SAE. SAE occurring in ≥ 2 patients were infective PEx of CR (n=8; 4.7%), ALT increased (n=2; 1.2%) and AST increased (n=2; 1.2%).

Possibly related SAEs occurred in 4 patients, with PT infection pulmonary exacerbation of CF (n=1), Dupuytren contracture (n=1) and Erythema Nodosum (n=1). The fourth subject experienced an SAE of combined elevation of increased of liver function tests (blood bilirubin, ALT, AST, GGT) (n=1), which led to prematurely discontinuation of the trial.

Part B

Five (10.0%) subjects had at least 1 SAE. SAEs occurring in ≥2 subjects were infective PEx of CF (n=5, 10.0%).

None of the reported SAE was considered related to study drug.

Death

During part A and part B: no deaths occurred.

Discontinuation

Part A:

Three (1.7%) subjects had AEs that led to treatment discontinuation, due to adverse events considered possibly related or related to the study medication. The study drug was withdrawn and all AEs were considered not resolved.

The adverse events leading to discontinuation were relapse of Multiple Sclerosis (n=1), combination of feeling fatigue/not feeling well and migraine (n=1) and an SAE of combined moderate blood BILI increased with severe ALT increased, severe AST increased, and severe GGT increased (n=1).

Part B

No subject had an AE leading to discontinuation of the drug.

Pregnancy

Part A

Six female subjects had a positive pregnancy test. The treatment was interrupted during the pregnancy in all, except one patient. This patient transitioned to a commercially available treatment. After the pregnancy, the treatment was resumed in one patient, while for the other subjects this is unknown. A total of 5 pregnancies were completed, and in 3 subjects a normal baby was born. The outcome of the other two pregnancies is not known.

Part B

No pregnancies were reported during the study.

Treatment interruption

Part A:

Twelve (7.0%) subjects had AEs that led to study drug interruption. AEs leading to treatment interruption most frequently occurred in the SOC investigations (n=7), followed by cardiac disorders (n=2), gastrointestinal disorders (n=2) and Skin and subcutaneous tissue disorders (n=2).

One patient experienced an episode of cardiac disorder of life-threatening intensity, considered not to be related to treatment. AEs by PT occurring in at least 2 subjects were ALT increased (n=4), AST increased (n=4), and blood BILI increased (n=3).

A total of 7 (4.1%) patients had a drug related AE leading to treatment interruption. Most events SOC Investigations (n=5), followed by the SOC Skin and Subcutaneous disorders (n=2). Drug related AEs by PT occurring in at least 2 subjects were ALT increased (n=3), AST increased (n=2). (Table 6)

Table 6: Related AEs leading to treatment interruption by SoC and PT (Part A, safety set)

System Organ Class Preferred Term	ELX/TEZ/IVA N = 172	
	n (%)	Events/100PY
Total duration of TE period for Part A in 100 PY	--	1.66
Subjects with any related AEs leading to study drug interruption	7 (4.1)	11.43
Investigations	5 (2.9)	6.01
Alanine aminotransferase increased	3 (1.7)	2.41
Aspartate aminotransferase increased	2 (1.2)	1.20
Blood bilirubin increased	2 (1.2)	1.20
Blood lactate dehydrogenase increased	1 (0.6)	0.60
Gamma-glutamyltransferase increased	1 (0.6)	0.60
Skin and subcutaneous tissue disorders	2 (1.2)	1.80
Erythema nodosum	1 (0.6)	1.20
Rash	1 (0.6)	0.60
Ear and labyrinth disorders	1 (0.6)	1.20
Hyperacusis	1 (0.6)	0.60
Tinnitus	1 (0.6)	0.60
Eye disorders	1 (0.6)	0.60
Vision blurred	1 (0.6)	0.60
General disorders and administration site conditions	1 (0.6)	0.60
Feeling abnormal	1 (0.6)	0.60
Psychiatric disorders	1 (0.6)	1.20
Anxiety	1 (0.6)	0.60
Mood altered	1 (0.6)	0.60

Part B

No subject interrupted study drug due to AEs.

Adverse events of special interest

Adverse events of special interest are elevated transaminases and rash.

Elevated transaminases

Part A

Overall, 12 (7.0%) subjects had at least 1 elevated transaminase event. Most events were mild (n=5) or moderate (n=6) in severity. Two (1.2%) subjects had events that were serious; 1 serious event was considered related.

One (0.6%) subject had an event that led to treatment discontinuation, and 5 (2.9%) subjects had events that led to treatment interruption.

In Part A, 11 subjects had elevated transaminase events that were assessed by the investigator as possibly related or related to study drug. Of these 11 subjects, study drug was interrupted in 4 subjects, of whom 1 also discontinued study drug.

Table 7: Summary of elevated transaminase events (Part A, safety set)

Category	ELX/TEZ/IVA N = 172	
PT	n (%)	Events/100PY
Subjects with any elevated transaminase events	12 (7.0)	22.25
ALT increased	9 (5.2)	12.63
AST increased	11 (6.4)	9.62
Subjects with any elevated transaminase events by maximum severity		
Mild	5 (2.9)	--
Moderate	6 (3.5)	--
Severe	1 (0.6)	--
Life-threatening	0	--
Missing	0	--
Subjects with elevated transaminase events leading to treatment discontinuation	1 (0.6)	1.20
Subjects with elevated transaminase events leading to treatment interruption	5 (2.9)	6.01
Subjects with serious elevated transaminase events	2 (1.2)	3.61
Subjects with related serious elevated transaminase events	1 (0.6)	2.41
Subjects with elevated transaminase events leading to death	0	0

Part B

Overall, 1 (2.0%) subject had at least 1 elevated transaminase event considered to be possibly related to medication. The event was mild in severity and nonserious and did not lead to treatment discontinuation or interruption.

Rash

Part A

Overall, 16 (9.3%) subjects had a rash event with a total of 6 being treatment related. All the rash events were mild (n=15) or moderate (n=1) in severity, and none were serious. No subject had a rash event that led to treatment discontinuation, and 1 (0.6%) subject had a mild, treatment related rash event that led to treatment interruption.

Part B

Overall, 4 (8.0%) subjects had a rash event. All events were mild in severity, and none were serious. No subject had a rash event that led to treatment discontinuation or interruption.

Lab values, vital signs ECG, pulse oximetry, and ophthalmologic examination

Liver function test (LFT)

Part A

Overall, six (3.5%) subjects had ALT or AST >3 × ULN, 3 (1.8%) subjects had ALT or AST >5 × ULN, and no subjects had ALT or AST >8 × ULN.

Overall, two (1.2) subjects had ALT or AST >3 × ULN and TBILI >2 × ULN. Of these, 1 (0.6%) subject had elevations that occurred at separate visits, and 1 (0.6%) subject had concurrent ALT or AST >3 × ULN and TBILI elevation >2 × ULN.

No causality assessment was made for the increase LFT identified by chemistry.

Part B

Most subjects (n=49) had ALT and AST values that remained ≤3 × ULN: One (2.0%) subject had ALT or AST >3 × ULN, and no subjects had ALT or AST >5 × ULN and ALT or AST >8 × ULN.

No causality assessment was made for the increased LFT identified by chemistry.

Chemistry

CK elevations

Part A

Overall, 5 (2.9%) subjects had CK >5 × to ≤10 × ULN, and 2 (1.2%) subjects had CK >10 × ULN . AEs of blood creatine phosphokinase increased occurred in 8 (4.7%) subjects, and no subject discontinued treatment due to an AE of blood creatine phosphokinase increased. The AEs of blood creatine phosphokinase increased were mild (n=6) or moderate (n=2) in severity.

Part B

Overall, 1 (2.0%) subject had CK >5 × to ≤10 × ULN, 1 (2.0%) subject had CK >10 × ULN.

AEs of blood creatine phosphokinase increased occurred in 2 (4.0%) subjects, no subject discontinued treatment due to an AE of blood creatine phosphokinase increased. Both AEs of blood creatine phosphokinase increased were mild in severity with one considered as unlikely and the other as considered likely related to study drug.

Other Chemistry tests

Part A and Part B

Apart from liver function tests and the CK elevations described above, there were no clinically relevant trends in mean values of other chemistry parameters. There were no clinically relevant trends in coagulation parameters in both parts.

Vital signs/Pulse oximetry ECG

There was no trend observed in Part A and B in the vital sign's parameters, pulse oximetry and ECG.

Ophthalmologic examination

Ophthalmologic examinations (OEs) were only conducted for the 51 subjects who were <18 years of age on the date of informed consent in a parent study. Three subjects did not have ophthalmologic examinations as the study visits were impacted by COVID-19.

Part A

Three (1.7%) subjects each had an AE of cataract; all AEs were mild and nonserious. Two AEs of cataract were assessed by the investigator as possibly related to study drug and 1 AE of cataract was assessed by the investigator as unlikely related to study drug. All AEs were ongoing at the time of reporting.

Part B

One subject had an AE of cataract; the AE was mild and nonserious. The AE of cataract was assessed by the investigator as unlikely related to study drug.

2.3.2. Discussion on clinical aspects

With this article 46 procedure, the MAH presented the final study results of Study VX19-445-115, a Phase 3b, open-label study in CF subjects 12 years of age and older, homozygous for *F508del* including patients who have completed the parent study VX18-445-109. Study VX19-445-115 is a stand-alone study.

Study VX19-445-115 included patients who completed the parent study VX18-445-109. Updates of sections 4.2, 4.4. and 4.8 of the SmPC as requested by the CHMP, were endorsed. These updates refer to clearer warnings referring to the risk of elevated ALT and AST and drug induced liver injury.

Study VX19-445-115 was designed to evaluate the long-term safety and tolerability up to 144 weeks of ELX/TEZ/IVA. The study has 2 parts, Part A and Part B. Homozygotic F/F Subjects aged ≥ 12 years were rolled over from the parent study VX18-445-109, where they were treated for 24 weeks with TEZ/IVA or ELX/TEZ/IVA. The study VX19-445-115 included up to 30% of patients aged 12-18 years.

The inclusion in part B was restricted to two countries which limited the included number of patients to 50. Part B and was prematurely terminated mainly because of the commercial availability of Kaftrio.

The investigated dose of ELX/TEZ/IVA is identical with the dose authorized for this population. Most subjects completed part A of the study. The reported median exposure of the safety set of Part A is 48 weeks, and for Part B 60.1 weeks. However, for about 50% of patients the actual exposure to ELX/TEZ/IVA might be longer, as they were exposed to treatment in the parent study.

Adverse events

Almost all patients experienced at least 1 adverse event (AE). Most AEs were of mild intensity and resembled the adverse event correlated to sign and symptoms of CF disease and the well-known adverse event profile of the triple combination.

The study has a single arm design, which may impair the interpretation of the safety results by the lack of a comparator arm. Nevertheless, no new safety events emerged, although the comparison with the parent study showed a higher frequency of SAE (15 % vs 6%) and treatment interruptions (7% vs 2%) and or transaminase elevations (7% vs 2%). These increased frequencies are likely to be attributed to the longer exposure time as the exposure adjusted rates, provided by the applicant in the response to supplementary information, were comparable with the ones reported in the previous studies.

Subgroup analysis by age (i.e. adolescents 12-18 years vs. adults ≥18 years) have not been presented. It is acceptable to pool results for adolescents and adults in line with previous procedures for ELX/TEZ/IVA, and no separate analysis per age group is requested (EMEA/H/C/005269/ P10 and 005269/P46/P09).

LFT are well known side effects of Kaftrio. The current SmPC section 4.8 mentions that this was only observed in the post-marketing period, but in Study VX19-445-115, one subject discontinued due to a SAE due to a possibly drug related increase in liver function tests (AST, ALT, GGT, bilirubin). Based on this event, the CHMP requested updates for section 4.2, 4.4 and 4.8 to provide a clearer warning to the risk of elevated transaminases and drug inducted liver injury.

Conclusion

This single arm, open label study provided additional long-term safety with a mean duration of approximately 48 weeks in Part A and 62 weeks in Part B for Kaftrio in a homozygous F/F CF population.

The currently provided data show that that the safety profile aligns with previously reported data, although a stronger warning about the risk of drug-induced transaminases is warranted.
The MAH should submit an appropriate variation within 30 days after finalisation of Art 46 WS procedures EMEA/H/C/005269/P46/013 and EMEA/H/C/005269/P46/014 to implement the agreed changes to the SmPC (sections 4.2, 4.4 and 4.8).

3. Rapporteur's overall conclusion and recommendation

Overall, the B/R of Kaftrio remains positive.

The SmPC needs to be updated, to emphasise the warning about the risk of drug induced elevated transaminases. The MAH should submit an appropriate variation within 30 days after finalisation of Art 46 WS procedures EMEA/H/C/005269/P46/013 and EMEA/H/C/005269/P46/014 to implement the agreed changes to the SmPC (sections 4.2, 4.4 and 4.8).

☒ Fulfilled:

No further action required; however, a variation should be submitted to implement the agreed changes to the SmPC (sections 4.2, 4.4 and 4.8). The MAH should commit to submit this variation application within 30 days after finalisation of Art 46 WS procedures EMEA/H/C/005269/P46/013 and EMEA/H/C/005269/P46/014.

☐ Not fulfilled:

4. Request for supplementary information

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

1. Almost all patients from the parent study VX18-445-109 rolled over to study VX19-445-115. Please clarify why 4 patients were not enrolled in Part A.
2. Only 50 patients rolled over to part B of the study. Please clarify why only N=50 patients were enrolled.
3. Please clarify the "other" reasons for discontinuation of the 4 patients in part B.

4. Please clarify why patients stopped because of the commercial availability of the drug, as this was not mentioned in the protocol as a stopping criterion.

5. The applicant is asked to provide a tabular overview in descending order of (possibly) drug related AE (By PT) occurring in ≥ 4 patients in part A of the trial.

6. The Applicant is asked to confirm if the subject with the SAE with a combined increase of liver functions is the same subject that discontinued the trial because of this drug related event.

7. The Applicant is asked to provide the possibly related drug related AE's leading to treatment interruption by SoC and PT of part A of the study.

8. No new safety events emerged, but compared with the parent study, a higher frequency of SAEs (15.% vs 5.9%), treatment interruptions (7% vs 2.3%) and elevated transaminases (7% vs 2.3%) were observed.

a) The applicant is asked to compare the exposure rates for these events with the parent study.

b) The applicant is asked to explain the higher frequency of SAE's and treatment interruption observed in study VX-115 compared with the parent study.

9. One patient experienced an SAE with a combined increase of liver functions, considered to be related to Kaftrio. The applicant is asked to confirm if this patient discontinued the trial and/or treatment.

10. The current SmPC section 4.8 only mentions that cases of treatment discontinuation due to elevated transaminases have been reported in the post marketing setting. As this case occurred during a study, an update to the SmPC might be necessary. Please find attached SmPC with the proposed updates. After agreement of the wording for the SmPC, the MAH is requested for a commitment to submit a variation shortly after finalisation of the procedure.

11. The current SmPC section 4.4 already includes a comment on regular transaminase monitoring. This section must slightly be reworded to provide a clearer/stronger warning about the risk of drug induced elevated transaminases. Consequently, a recommendation in section 4.2.is proposed as well. Please find attached SmPC with the proposed updates. After agreement of the wording for the SmPC, the MAH is requested for a commitment to submit a variation shortly after finalisation of the procedure.

12. The applicant is asked to provide a tabular overview in descending order of (possibly) drug related AEs (By SOC and PT) leading to treatment interruptions.

13. AESI are "Elevated transaminases". As elevations of transaminases often occur, the applicant is asked also to describe the (possibly) related drug events and if the events leaded to discontinuations or interruption (for both part A and part B). A reference to listing 16.2.7.1a is not accepted.

14. The section "liver function test" of part A and B does not mention the relation with Kaftrio. The Applicant is asked to provide this relation of the reported LFTs mentioned in this section as elevated transaminases occur frequently in CF.

15. Please indicate if the rash events reported in part A and part B were related to Kaftrio. It is not accepted to make a reference to table 14.3.1.4a.

16. Please discuss if for one patient the drug related transaminases were related to treatment by using the RUCAM scale.

17. Not all patients in part A had an ophthalmologic examination. Listing 16.2.8.8.3a displays the results of 48 patients, while the total study included 172 patients. Please clarify.

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

MAH responses to Request for supplementary information

Question 1

Almost all patients from the parent study VX18-445-109 rolled over to study VX19-445-115. Please clarify why 4 patients were not enrolled in Part A.

Summary of the Applicant's Response

The 4 subjects who did not rollover from parent study VX18-445-109 (Study 109) into

open-label extension (OLE) study VX19-445-115 (Study 115) because all discontinued from parent

Study 109 i.e.

- 1 subject was randomized but never dosed in the Treatment Period of Study 109, as they met exclusion criteria due to a change in clinical status (adverse event [AE] of infective pulmonary exacerbation [PEx]of cystic fibrosis [CF]).
- The three other subjects discontinued treatment and the study due to AEs in Study 109. These events were SAEs of anxiety/depression in the triple combination group and psychotic disorder and obsessive-compulsive disorder in the control arm.

Assessment of the Applicant's Response

The applicant clarified why the 4 subjects did not roll over from the parent study to study VX18-445-109.

Conclusion: issue resolved.

Question 2
Only 50 patients rolled over to part B of the study. Please clarify why only 50 patients were enrolled.

Summary of the Applicant's Response

Part B of Study 115 was only conducted in Australia and Belgium. Of the 50 subjects from Australia and Belgium who participated in Part A, a total of 49 completed Part A and also participated in Part B One subject moved countries during Part A of this study and continued participation in Part B.

Assessment of the Applicant's Response

The Applicant clarified that Part B of the study was limited to Australia and Belgium and except for one, all patients rolled over to part B of the study. Part A of the study took also place in Germany and the United Kingdom. Most of the 172 included patients were from the UK and Germany.

Conclusion: issue resolved.

Question 3

Please clarify the "other" reasons for discontinuation of the 4 patients in part B.

Summary of the Applicant's Response

The 4 subjects discontinued from the study to transition to a managed access program (MAP).

Assessment of the Applicant's Response

Various definitions of managed access programme exist. Most definitions state that a patient can get access for an investigational or non-approved product when the patient who cannot enrol in an ongoing clinical trial and the product is not approved. However, these 4 patients were included in an ongoing clinical trial and discontinued because of transition of a managed access program, a program, designed for patients who are not fit for inclusion in a clinical trial. This seems somewhat contradictory.

Conclusion: issue partly clarified but will not be further pursued.

Question 4

Please clarify why patients stopped because of the commercially availability of the drug, as this was not mentioned in the protocol as a stopping criterion.

Summary of the Applicant's Response

As specified in Study 115 Protocol Versions 1.0 (global protocol) and 2.2 AU and BE, "Subjects may withdraw from the study at any time at their own request." While commercial availability was not expressly mentioned in the protocol as a stopping criterion, discontinuation from the study for any reason is always at the discretion of the investigators and subjects/subjects' caregivers. If subjects/subjects' caregivers expressed a desire to transition to commercial Trikafta/Kaftrio once available in their country, they were allowed to do so.

Assessment of the Applicant's Response

We agree with the Applicant, that the patients are allowed to discontinue from study participation at their request. A total of 46 (92%) of study part B stopped because the product had become commercially available and the patients had thus access to treatment outside the clinical trial. Nevertheless, this reported number for this stopping criterium appears to be high, considering that the trial burden is low, the treatment is well tolerated and the study drugs will be provided at no costs during the trial.

We also agree with the Applicant that Investigator's are also allowed to discontinue the study participation for any reasons. This reason normally refers to safety measures and investigators usually do not discontinue study participation when the drug is commercially available.

Conclusion: issue clarified.

Question 5

The applicant is asked to provide a tabular overview in descending order of (possibly) drug related AE (By PT) occurring in ≥ 4 patients in part A of the trial.

Summary of the Applicant's Response

Table 8 provides an overview of related and possibly related AEs by preferred term (PT).

Table 8 Overview of related and possibly related AEs by preferred term (PT)

	ELX/TEZ/IVA N = 172	
Preferred Term	**n (%)**	**Events/100PY**
Total duration of treatment-emergent period for Part A in 100 PY	--	1.66
Subjects with any related AEs	69 (40.1)	132.29
Headache	10 (5.8)	8.42
Sputum increased	10 (5.8)	6.01
Aspartate aminotransferase increased	9 (5.2)	7.22
Blood bilirubin increased	9 (5.2)	6.61
Alanine aminotransferase increased	8 (4.7)	10.22
Cough	7 (4.1)	5.41
Abdominal pain upper	6 (3.5)	4.81
Blood creatine phosphokinase increased	6 (3.5)	3.61
Diarrhea	5 (2.9)	7.22
Abdominal pain	5 (2.9)	5.41
Rash	5 (2.9)	3.61
Fatigue	5 (2.9)	3.01
Hyperbilirubinemia	4 (2.3)	2.41

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; PY: patient-year; TEZ: tezacaftor
Notes: MedDRA Version 24.0 was used. Events/100PY: number of events per 100 patient years (336 days=48 weeks per year) = number of events/total duration of treatment-emergent period for Part A in 100PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted.

Assessment of the Applicant's Response

The Applicant provided the requested table. The reported drug related adverse events aligns with previous reported events.

Conclusion: issue resolved

Question 6

The Applicant is asked to confirm if the subject with the SAE with a combined increase of liver functions is the same subject that discontinued the trial because of this drug related event.

Summary of the Applicant's Response

Vertex confirms that this is the same subject.

Assessment of the Applicant's Response

The Applicant confirmed the this was the same subject.

Conclusion: issue resolved.

Question 7

The Applicant is asked to provide the possibly related drug related AE's leading to treatment interruption by SoC and PT of part A of the study.

Summary of the Applicant's Response

Table 9 provides the related and possibly related AEs leading to treatment interruption by System Organ Class (SOC) and PT of Part A.

Table 9 Related AEs Leading to Treatment Interruption by SOC and PL 9 (Part A, Safety Set)

System Organ Class Preferred Term	ELX/TEZ/IVA N = 172 n (%)	 Events/100PY
Total duration of TE period for Part A in 100 PY	--	1.66
Subjects with any related AEs leading to study drug interruption	7 (4.1)	11.43
Investigations	5 (2.9)	6.01
Alanine aminotransferase increased	3 (1.7)	2.41
Aspartate aminotransferase increased	2 (1.2)	1.20
Blood bilirubin increased	2 (1.2)	1.20
Blood lactate dehydrogenase increased	1 (0.6)	0.60
Gamma-glutamyltransferase increased	1 (0.6)	0.60
Skin and subcutaneous tissue disorders	2 (1.2)	1.80
Erythema nodosum	1 (0.6)	1.20
Rash	1 (0.6)	0.60
Ear and labyrinth disorders	1 (0.6)	1.20
Hyperacusis	1 (0.6)	0.60
Tinnitus	1 (0.6)	0.60
Eye disorders	1 (0.6)	0.60
Vision blurred	1 (0.6)	0.60
General disorders and administration site conditions	1 (0.6)	0.60
Feeling abnormal	1 (0.6)	0.60
Psychiatric disorders	1 (0.6)	1.20
Anxiety	1 (0.6)	0.60
Mood altered	1 (0.6)	0.60

Source: Ad hoc Table 1
AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: preferred term; PY: patient-year; SOC: System Organ Class; TE: treatment-emergent; TEZ: tezacaftor
Notes: MedDRA Version 24.0 was used. Events/100PY: number of events per 100 patient years (336 days=48 weeks per year) = number of events/total duration of treatment-emergent period for Part A in 100PY. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted. Table is sorted in descending order of ELX/TEZ/IVA by SOC, and by PT within each SOC.

Assessment of the Applicant's Response

The Applicant provided the requested table. Most drug related treatment interruptions were due to elevation of the hepatic enzymes and bilirubin. These are well known side effects of Kaftrio as well as occurring as symptom of CF.

Conclusion: issue resolved.

Question 8

No new safety events emerged, but compared with the parent study, a higher frequency of SAEs (15.% vs 5.9%), treatment interruptions (7% vs 2.3%) and elevated transaminases (7% vs 2.3%) were observed.

a) The applicant is asked to compare the exposure rates for these events with the parent study.

b) The applicant is asked to explain the higher frequency of SAE's and treatment interruption observed in study VX-115 compared with the parent study.

Summary of the Applicant's Response

Table 10 provides a comparison of exposure to ELX/TEZ/IVA for subjects in parent **Study 109** and OLE Study 115 Part A. The mean (SD) exposure in Study 109 was 23.7 (1.9) weeks for the 87 subjects in the ELX/TEZ/IVA group, and in Study 115 was 46.0 (7.4) weeks for the 172 subjects in Part A. Given that the mean exposure was nearly twice as long in Study 115, it is not unexpected that SAEs and treatment interruptions occurred at a higher frequency than in Study 109.

To provide additional context for the SAEs and treatment interruption, the exposure-adjusted event rate (events/100 patient years [PY]) for SAEs and AE leading to treatment interruption in pivotal study **VX17-445-102 (Study 102) and its OLE VX17-445-105** (Study 105) Week 96 analysis were as follows:

- Study 102 ELX/TEZ/IVA arm: SAEs = 36.93, AE leading to treatment interruption = 25.95
- Study 102 placebo arm: SAEs = 67.05, AE leading to treatment interruption = 14.01
- Study 105: SAEs = 22.48, AE leading to treatment interruption = 7.61

Taken in context, the exposure rates in Study 115 Part A are within the range seen in prior studies with ELX/TEZ/IVA, and do not suggest any new safety concern.

Table 10 Summary of Exposure in Study 109 (Safety Set for the Treatment period) and Study 115 Part A (Safety Set)

Category	ELX/TEZ/IVA			
	Study 109 N = 87		Study 115 N = 172	
		Events/100 PY		Events/100 PY
Total duration of TE Period in 100 PY	--	0.43	--	1.66
Total exposure (patient weeks)	2062.7	--	7910.1	--
Mean (SD) exposure duration (weeks)	23.7 (1.9)	--	46.0 (7.4)	--
SAEs, n (%)	5 (5.7)	16.17	26 (15.1)	27.06
AE leading to treatment interruptions, n (%)	2 (2.3)	13.86	12 (7.0)	19.24
AESI of elevated transaminase, n (%)	6 (6.9)	32.33	12 (7.0)	22.25

Source: Study 109 CSR/Tables 14.1.7, 14.3.2.2, 14.3.2.5, Ad hoc Table 14.3.1.1, Ad hoc Table 14.3.2.8 and Study 115 CSR/Table 14.1.7a, Table 14.3.2.2a, Table 14.3.2.5a, Table 14.3.2.7a

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

Notes: Events/100PY was defined as the number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of treatment-emergent period in 100PY. 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 any interruptions in dosing. MedDRA Version 23.0 was used for Study 109 and Version 24.0 was used for Study 115.

Assessment of the Applicant's Response

The median exposure time in the open label extension study VX115 was twice as long as in the parent study VX 109. We agree with the applicant that the longer exposure time may likely contribute to the numerically higher observed frequency of n the OLE compared with the parent study.

The exposure adjusted event rate adjusts for the difference in the exposure time. The exposure adjusted SAE and AEs leading to interruption were provided to contextualise these events for study VX17-445-002, VX17-445-005, VX17-445-109 and VX17-445-115. Study VX 17-0445-002 was the

pivotal study conducted in CF subjects with F/MF of 12 years and older. Study VX17-445-005 (OE 005) was an open label extension study in CF subjects aged 12 years and older with F/MF (002) and FF/FF (003) (see Table 11).

Table 11: Summary of the exposure adjusted event rate for SAE, AE leading to interruption and AE elevated transaminase for study VX-109, VX-115, VX-002 and VX-005.

Study	**VX-109**	**VX-115**	**VX-002**		**VX-005**
			ELZ/TEZ/IVA	**Placebo**	
	Events/ 100 PY	**Events/ 100 PY**	**Events/ 100 PY**	**Events/ 100 PY**	**Events/ 100 PY**
SAE	16.7	27.06	36.93	67.05	24.48
AE leading to interruption	13.36	19.24	25.95	14.01	7.61
AE elevated transaminases	32.33	22.25	NR	NR	NR

The exposure adjusted AE elevated transaminase is numerically smaller in the OLE 105 compared with the parent study VX-109. Although the exposure adjusted SAE and AEs is higher for study VX-115 compared with the parent study VX-109, the events align with the previous data reported in study VX-002 and VX-005.

Conclusion: issue resolved.

Question 9

One patient experienced an SAE with a combined increase of liver functions, considered to be related to Kaftrio. The applicant is asked to confirm if this patient discontinued the trial and/or treatment.

Summary of the Applicant's Response

Vertex confirms that Subject 109-712-004 had SAEs of blood bilirubin increased, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, and gamma-glutamyl transferase (GGT) increased on Day 289 leading to study drug discontinuation, and subsequently discontinued from the study on Day 338.

Assessment of the Applicant's Response

The Applicant confirmed that one patient discontinued the trial of drug related increase in liver functions.

Conclusion: issue resolved

Comment 10

The current SmPC section 4.8 only mentions that cases of treatment discontinuation due to elevated transaminases have been reported in the post marketing setting. As this case occurred during a study, an update to the SmPC might be necessary. Please find attached SmPC with the proposed updates.

After agreement of the wording for the SmPC, the MAH is requested for a commitment to submit a variation shortly after finalisation of the procedure.

Summary of the Applicant's response :

Vertex agrees to update Section 4.8 of the Summary of Product Characteristics (SmPC); proposed changes are included in the attached SmPC.

Assessment of the Applicant's Response

See SmPC assessment.

Conclusion: see SmPC assessment

Comment 11

The current SmPC section 4.4 already includes a comment on regular transaminase monitoring. This section must slightly be reworded to provide a clearer/stronger warning about the risk of drug induced elevated transaminases. Consequently, a recommendation in section 4.2.is proposed as well. Please find attached SmPC with the proposed updates. After agreement of the wording for the SmPC, the MAH is requested for a commitment to submit a variation shortly after finalisation of the procedure.

Summary of the Applicant's response:

Vertex agrees to update Sections 4.2 and 4.4 of the SmPC to more clearly address the risk of elevated transaminases; proposed changes are included in the attached SmPC.

Assessment of the Applicant's Response

See SmPC assessment.

Conclusion: see SmPC assessment.

Comment 12

The applicant is asked to provide a tabular overview in descending order of (possibly) drug related AEs (By SOC and PT) leading to treatment interruptions.

Summary of the Applicant's Response:

Please see Table 9 for the related and possibly related AEs leading to treatment interruption by SOC and PT of Part A. There were no AEs leading to treatment interruption in Part B.

Assessment of the response

We agree that this question is a repetition of Question 8. Please refer to question 8.

Conclusion issue resolved.

Question 13

AESI are "Elevated transaminases". As elevations of transaminases often occur, the applicant is asked also to describe the (possibly) related drug events and if the events leaded to discontinuations or interruption (for both part A and part B). A reference to listing 16.2.7.1a is not accepted.

Summary of the Applicant's Response

In Part A, 11 subjects had elevated transaminase events that were assessed by the investigator as possibly related or related to study drug. Of these 11 subjects, study drug was interrupted in 4 subjects, 1 of whom also discontinued study drug (Listing 16.2.7.2a).

In Part B, 1 subject had an elevated transaminase event that was assessed by the investigator as possibly related to study drug and did not lead to treatment discontinuation or interruption (Listing 16.2.7.2b).

Assessment of the Applicant's Response

The applicant provided the requested data.

Conclusion: issue resolved

Question 14

The section "liver function test" of part A and B does not mention the relation with Kaftrio. The Applicant is asked to provide this relation of the reported LFTs mentioned in this section as elevated transaminases occur frequently in CF.

Summary of the Applicant's Response

The section "Liver Function Tests" for Part A and B in the CSR does not describe the relationship of study drug to the reported LFTs because the investigator assigns a relationship of the study drug to an AE (per Study 115 Protocol Versions 1.0 and 2.2 AU and BE/ Section 13.1.1.5), and not to observed LFT values.

AEs of transaminase elevation and their relationship to study drug are reported in separate sections describing AEs (Study 115 CSR/Sections 12.1.3.6 [Part A] and 12.2.3.6 [Part B]).

Assessment of the Applicant's Response

Not all lab abnormalities are noted as adverse events by the investigators. Lab abnormalities including liver function test abnormalities can be due drug related.

Nevertheless, LFT are well known side effects and the Applicant agreed to update the SmPC to address the risk of elevated LFT more clearly. Therefore, this issue will not be further pursued.

Conclusion: issue partly resolved, will not be further pursued.

Question 15

Please indicate if the rash events reported in part A and part B were related to Kaftrio. It is not accepted to make a reference to table 14.3.1.4a.

Summary of the Applicant's Response

A summary of rash events (adverse event of special interest [AESI]) by PT and by strongest relationship is presented in Table 12. In both Parts A and B, all rash events were mild or moderate in severity, and none were serious.

Table 12 Summary of AESI (Rash Events) by PT and by Strongest Relationship (Parts A and B, Safety Set)

	ELX/TEZ/IVA	
PT **Strongest Relationship**	**Part A** **N = 172**	**Part B** **N = 50**
Subjects with any Rash, n (%)	16 (9.3)	4 (8.0)
Dermatitis allergic	0	1 (2.0)
Not related	0	0
Unlikely related	0	1 (2.0)
Possibly related	0	0
Related	0	0
Rash	12 (7.0)	2 (4.0)
PT **Strongest Relationship**	**Part A** **N = 172**	**Part B** **N = 50**
Not related	3 (1.7)	2 (4.0)
Unlikely related	4 (2.3)	0
Possibly related	4 (2.3)	0
Related	1 (0.6)	0
Rash erythematous	1 (0.6)	0
Not related	0	0
Unlikely related	1 (0.6)	0
Possibly related	0	0
Related	0	0
Rash papular	2 (1.2)	0
Not related	0	0
Unlikely related	1 (0.6)	0
Possibly related	1 (0.6)	0
Related	0	0
Urticaria	1 (0.6)	1 (2.0)
Not related	0	0
Unlikely related	1 (0.6)	1 (2.0)
Possibly related	0	0
Related	0	0

Sources: Study 115 CSR/Table 14.3.1.4a, Table 14.3.1.4b, Table 14.3.2.8a, and Table 14.3.2.8.b

AE: adverse event; AESI: adverse event of special interest; ELX: elexacaftor; IVA: ivacaftor; N: total sample size; PT: preferred term; TEZ: tezacaftor

Notes: MedDRA Version 24.0 was used in Part A and Version 25.1 was used in Part B. A subject with multiple events within a category was counted only once under the strongest relationship in that category. An AE with relationship missing was counted as Related.

Assessment of the Applicant's Response

A total of 6 rash events were considered to be (possibly) drug related. All events were of mild severity.

One subject experience a rash event of moderate severity. This event was not considered to be treatment related.

Conclusion: issue resolved.

Question 16

Please discuss if for one patient the drug related transaminases were related to treatment by using the RUCAM scale.

Summary of the Applicant's Response

The AEs of ALT and blood bilirubin increased were assessed by the investigator as **possibly related**. The Roussel Uclaf Causality Assessment Method (RUCAM) scale was not used by investigators.

Assessment of the Applicant's Response

During the study, per protocol, the investigators were asked to provide narratives if the following was present (a) ALT or AST elevation >5 × ULN or (b) if ALT or AST >3 × ULN with concurrent total bilirubin >2 × ULN were present. The narratives for 3 patients were provided, with one being considered correlated to treatment while another was considered not being correlated. The causality for this patient was missing. The Applicant now provided the causality, and this event appears to be related to treatment by investigators. The RUCAM scale was not used to assess the causality.

Conclusion: issue resolved.

Question 17

Not all patients in part A had an ophthalmologic examination. Listing 16.2.8.8.3a displays the results of 48 patients, while the total study included 172 patients. Please clarify.

Summary of the Applicant's Response

Per Study 115 Protocol Versions 1.0 and 2.2 AU and BE/Section 11.2.7, ophthalmologic examinations (OEs) were only conducted for subjects who were <18 years of age on the date of informed consent in a parent study. This included 51 subjects in Study 115.The 3 subjects who did not have OEs in the database were due to study visits being impacted by COVID-19. Furthermore, for these subjects, an OE was only required at the Early Termination of Treatment Visit or Week 48 Visit (whichever comes first) for subjects who had received at least 12 weeks of study drug (in a parent study and Study 115) since their last OE.

Assessment of the Applicant's Response

The Applicant clarified that Ophthalmologic examination were only conducted in subjects < 18 year on the date of informed consent of the parent study 115. This included a total of 51 patients; 3 examinations did not take place as the study visits were being impacted by COVID-19.

Conclusion: issue resolved.