9 November 2023
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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/P46/013

Note

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

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Table of contents

1. Introduction

On 01 June 2023, the MAH submitted a completed paediatric study VX20-445-121 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 VX20-445-121. Study VX20-445-121 is a Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Subjects with Cystic Fibrosis heterozygous for F508 del and a minimal function mutation (F/MF genotypes) who are 12 years of age or older and who participated in either parent studies (VX19-445-117 or VX20-445-126). Study VX19-445-117 and Study VX20-445-126 have been previously reviewed in EMA/H/C/00529/0010/P46 and EMEA/H/C/005269/0009/P46 respectively.

The MAH stated that study VX20-445-121 is like the parent studies a stand-alone study. The parent studies were submitted with previous Article 46 procedures (EMA/H/C/00529/0010/P46 and EMEA/H/C/00529/0009/P46) respectively and are currently still under review.

2.2. Information on the pharmaceutical formulation used in the study

In Study VX20-445-121, 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 final report(s) for study VX20-445-121.

Clinical study number and title

Study VX20-445-121 (Study 121) was a Phase 3b, multicentre, open-label study evaluating the safety of elexacaftor/tezacaftor/ivacaftor combination therapy in subjects with cystic fibrosis.

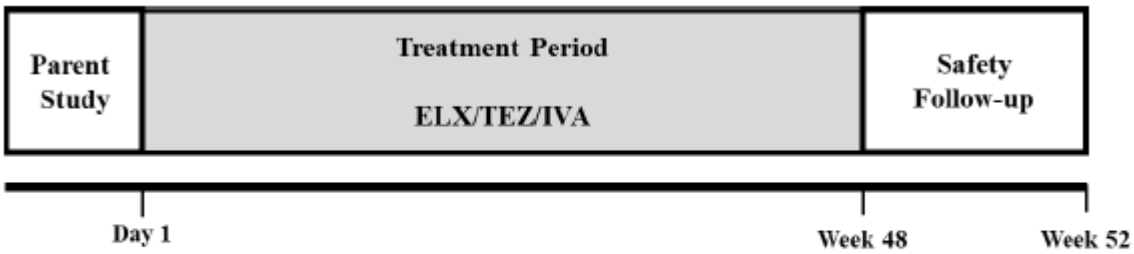
Description

Study VX20-445-121 was a Phase 3b, multicenter, open-label study in CF subjects aged ≥ 12 years who are heterozygous for the F508del mutation and a Minimal Function mutation (F/MF) and who completed a parent study (VX19-445-117 [Study 117] or VX20-445-126 [Study 126]).

The primary objective was to evaluate the safety and tolerability of ELX/TEZ/IVA in subjects with heterogenous F508 and MF mutation.

The planned study duration was approximately 52 weeks (from the first dose of study drug in this study), including a 48-week Treatment Period and a 4-week Safety Follow-up Period. The study design is depicted in figure 1 below.

Figure 1 Study 121 Study Design



Source: Study 121 aCSR/Figure 9-1
ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor
Note: Figure is not drawn to scale.

Methods

Study participants

The study included CF patients aged ≥ 12 years with an F/MF CFTR genotype who completed a parent study (Study 117 or Study 126) and met the following additional eligibility criteria.

Table 1: Key in-and exclusion criteria

Inclusion	Exclusion
Met at least 1 of the following criteria: - Completed study drug treatment in a parent study - Had study drug interruption(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 being considered for resumption of participation in this study after enrolling in another Vertex study of investigational CFTR modulators (referred to as "another qualified Vertex study"): Completed the Early Termination of Treatment (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. - Did not withdraw consent from a parent study -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. - History of drug intolerance in a parent study that would pose an additional risk to the subject - Pregnant and breast-feeding females - Current participation in an investigational drug trial other than a parent 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, o Subject had access to commercially available ELX/TEZ/IVA or was receiving managed-access program- supplied ELX/TEZ/IVA, or o Subject departed this study more than once to participate in another qualified Vertex study

Sources: Study 121 Protocol/Sections 8.1 and 8.2
CF: cystic fibrosis; ELX: elexacaftor; ETT: Early Termination of Treatment; IVA: ivacaftor; TEZ: tezacaftor

Assessor's comment

Study VX-445-117 and study VX-445-126 were Phase 3b, open-label, single arm studies in CF subjects 12 years of age and older, heterozygous for *F508del* and a Minimal Function mutation (F/MF genotypes).

The patients included in study VX-117 had to have an abnormal glucose tolerance at screening, while the included patients in study VX-126 had to have an FEV1 between 30% and 90% of predicted mean value.

After a screening period, patients were open-label treated for 13 weeks (study VX-126) or 48 weeks study VX-117), with the opportunity to enroll in the open label extension study VX-121, resulting in a longer pre-treatment duration for the patients from study VX-117 before inclusion of the trial VX20-445-121. For those who did not enroll in the open label study, a safety follow up was conducted within 28 days after the last dose of study drug.

Treatments

Study drug tablets were administered orally as ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Subjects 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 heterozygotic F508/MF subjects with CF.

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 160 subjects were expected to enroll in this open-label extension study.

Randomisation and blinding

Not applicable. This was an interventional open-label study.

Statistical Methods

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

Conduct of the trial

GCP

The study was conducted following GCP.

Amendments

The original protocol was dated 13 April 2021. The study was amended once (14 Feb 2022) to (1) remove parent study VX19-445-114 and to update the number of planned subjects and (2) Updated that study drug does not need to be discontinued for a male subject whose female partner becomes pregnant during study participation.

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 was included on 14 Jan 2022; the last patient last visit was on 20 Dec 2022. The study was conducted in Australia, Belgium, Canada, Czech Republic, and Spain.

A total of 86 subjects were enrolled. This was lower than the planned number because not all subjects of the parent studies elected to continue to the separate open-label study.

None of the study subjects completed the planned 48-week Treatment Period mainly because most subjects (75 [87.2%] subjects) elected to discontinue treatment due to commercial drug availability, while a total of 10 patients were enrolled in another qualified Vertex trial (Table 2).

One patient discontinued the study because of an AE

Table 2: Subject Disposition – All Subjects Set

Disposition/Reason	ELX/TEZ/IVA n (%)
All Subjects Set	86
Safety Set	86
Completed treatment	0
Discontinued treatment	86 (100.0)
Reason for discontinuation of treatment	
AE	1 (1.2)
Commercial drug is available for subject	75 (87.2)
Other	10 (11.6)
Completed study	0
Discontinued study	86 (100.0)
Reason for discontinuation from study	
Commercial drug is available for subject	76 (88.4)
Other	10 (11.6)
Subject who enrolled in another qualified Vertex study	10 (11.6)
Subject who enrolled in another qualified Vertex study and resumed participation in this study	0

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor
Note: All Subjects Set is defined as all subjects who were enrolled (defined as subject having data in the clinical database) in this study. Safety Set is defined as all subjects who have received at least 1 dose of study drug in this study. Percentages are calculated relative to the number of subjects in the Safety Set.

Recruitment

Baseline data

A total of 86 patients were included. The mean age at parent study baseline was 25.3 years, and 43.0% of the subjects were female. Most subjects (91.9%) were White, and 12.8% were Hispanic or Latino. The study included 27 subjects aged 12-18 years (31%). 31 subjects (36%), of whom 10 aged 12-18 years, were recruited from parent study VX19-445-117. 55 subjects (64%), of whom 17 aged 12-18 years, were recruited from parent study VX20-445-126.

The mean (SD) FEV1 was 67.6 (17.8) %. The mean (SD) safety baseline values were 116.6 (11.6) mm Hg for Systolic blood pressure (SBP) and 71.9 (9.4) mm Hg for Diastolic Blood pressure (DBP).

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

Efficacy results

Not applicable.

Number analysed

The safety set included a total of 86 subjects received at least 1 dose of ELX/TEZ/IVA during the study.

Safety results

Exposure

The mean exposure duration during the study was 20.2 weeks (range: 5.6 to 36.1 weeks), representing 1733.4 patient-weeks of exposure.

General description AE profile

In total, 61 (70.9%) subjects had at least 1 adverse event (AE). Most subjects had AEs that were mild (34 [39.5%] subjects) or moderate (23 [26.7%] subjects) in severity. Four (4.7%) subjects had 1 or more severe AEs. There were no deaths (Table 3).

Table 3: Overview of AEs – Safety Set

	ELX/TEZ/IVA N = 86 n (%)
Number of AEs (total)	154
Subjects with any AEs	61 (70.9)
Subjects with AEs by maximum severity	
Grade 1/Mild	34 (39.5)
Grade 2/Moderate	23 (26.7)
Grade 3/Severe	4 (4.7)
Grade ≥ 4 /Life-threatening/ Death	0
Subjects with AEs leading to study drug discontinuation	1 (1.2)
Subjects with AEs leading to study drug interruption	1 (1.2)
Subjects with Grade 3/4/5 AEs	4 (4.7)
Subjects with related AEs	10 (11.6)
Subjects with SAEs	4 (4.7)
Subjects with related SAEs	1 (1.2)
Subjects with AEs leading to death	0

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; N: total sample size; n: size of subsample; SAE: serious adverse event; TEZ: tezacaftor. Notes: MedDRA Version 25.1 was used

Adverse events

The most common AEs (occurring in ≥10% of subjects overall) were COVID-19 (n=16 (18.6%), infective pulmonary exacerbation of CF (n=11 (12.8%)), and nasopharyngitis n=9 (10.5%)).

Related AE

A total of 10 patients had a related AE; 1 patient had a related SAE (see section SAE) .

The related AEs were mostly found in the SOC investigations (n=7) and referred to alanine transaminase (ALT) increased (n=2), aspartate transaminase (AST) increased (n=2), blood creatinine kinase (CK) increased (n=2), blood bilirubin increased (n=1), blood unconjugated bilirubin increased (n=1) and gamma GT increased (n=1) and platelet count decreased (n=1).

The SOC hepatobiliary disorders also included 2 related events i.e. cholestasis (n=1) and hyperbilirubinemia (n=1).

SAEs and death

There were 4 (4.7%) subjects who had at least 1 SAE. SAEs of gastroenteritis viral, malnutrition, and anxiety occurred in 1 subject each; 1 subject had SAEs of ALT increased and AST increased.

All SAEs were considered not to be related to study medication, except for the SAEs of ALT increased and AST increased that occurred in the same subject. The observed ALT- and AST elevations were >8 ULN, while the liver biopsy revealed compatibility with a drug-induced liver injury. These events were considered mild in severity by the investigator. They led to treatment discontinuation. The elevated liver enzymes returned to baseline value during follow up.

Discontinuation

One subject had related SAEs of ALT increased and AST increased (see also section SAEs and death, and AESI: Elevated transaminases).

Treatment interruption

One subject had unlikely related moderate to severe AEs of ALT increased, AST increased, and blood creatine phosphokinase (CK) increased leading to treatment interruption. These adverse events resolved without treatment.

Adverse events of specific interests

Adverse events of specific interest are elevated transaminases and rash.

AESI: Elevated transaminases

A total of 5 (5.8%) subjects experienced an adverse event of elevated transaminases. Most events were considered of mild intensity. One subject had unlikely related events of severe AST increased and moderate ALT increased, which resulted in study drug interruption (Table 4).

A total of 3 (3.5%) subjects had a treatment-emergent elevated transaminase event, with 2 related and 1 unlikely related as determined by the investigator. Of these 3 subjects, 2 had 4 events that were considered mild and the dose was not changed. The other subject had 2 events were considered mild according to the investigator,but led to drug discontinuation (Table 4, see also section SAE).

Table 4: Elevated Transaminase Events (All Subjects Set)

Subject	PT	Severity	Action taken		Relationship to study drug
[redacted]	ALT increased	Mild	Dose not changed	Dose not changed	Not related
[redacted]	ALT increased	Moderate	Drug interrupted	Drug interrupted	Unlikely related
	AST increased	Severe	Drug interrupted	Drug interrupted	Unlikely related
[redacted]	ALT increased	Mild	Dose not changed	Dose not changed	Possibly related
[redacted]	ALT increased	Mild	Dose not changed	Dose not changed	Related
	AST increased	Mild	Dose not changed	Dose not changed	Related
[redacted]	ALT increased	Mild	Drug withdrawn	Drug withdrawn	Related
	AST increased	Mild	Drug withdrawn	Drug withdrawn	Related

ALT: alanine transaminase; AST: Aspartate Transaminase ,PT : preferred term

Adverse events were coded using MeDRA version 25.1. Severity assessment by the Investigator.

AESI: Rash

No subjects had a rash event during the study. One subject (1%) experienced a mild rash during the parent study; the rash was considered unlikely related to study medication.

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

Liver function tests

Most subjects had ALT/AST values that remained within the normal range. Three (3.5%) subjects had ALT or AST >3 × ULN, 1 (1.2%) subject had ALT or AST >5 × ULN, and 1 (1.2%) subject had ALT or AST >8 × ULN. No subject had elevations of ALT or AST >3 × ULN concurrent with newly occurred elevation of TBILI >2 × ULN.

Blood bilirubin

Most subjects had bilirubin values that remained within the normal range. Overall, 8.1% of the subjects had an elevation in total bilirubin (TBILI) >2 × to ≤3 × ULN, and 1 (1.2%) subject had an elevation in TBILI >3 × to ≤10 × ULN.

Creatinine kinase

AEs of blood creatine phosphokinase (CK) increased occurred in 3 (3.5%) subjects, no subject discontinued treatment due to this AE. One (1.2%) subject had a severe, unlikely related AE of blood CK increased leading to study drug interruption.

CHMP comment

As usual, no cause was reported for the reported lab deviations. The reported deviations are in line with previous reported data.

Vital signs

Mean SBP and DBP and pulse rate were variable over time. No specific trends were observed.

There were 5 (5.8%) subjects with SBP >140 mm Hg, and no subject with SBP >160 mm Hg; There were 2 (2.3%) subjects with DBP >90 mm Hg, and no subject with DBP >100 mm Hg.

One subject had an unrelated AE of hypertension of mild intensity considered not to be related to medication.

ECG

The ECG conducted at baseline and at the end of the study did not reveal a specific trend.

Ophthalmologic examination

Ophthalmologic examinations were only conducted for the 27 subjects who were <18 years of age on the date of informed consent in a parent study. No subject had a treatment emergent AE of cataract.

2.3.2. Discussion on clinical aspects

With this article 46 procedure, the MAH presented the final study results of Study VX20-445-121, a Phase 3b, open-label study in CF subjects 12 years of age and older, heterozygous for *F508del* and a minimal function mutation (F/MF genotypes).

Study 121 included patients who completed the parent study VX19-445-117 and VX20-445-126. Updates of sections 4.2, 4.4. and 4.8, as requested by the CHMP, were adopted by the Applicant. These updates were regarding the risk of elevated ALT and AST and drug induced liver injury.

Study VX121 was designed to evaluate the long-term safety and tolerability (48 weeks) of ELX/TEZ/IVA. However, interpretation of obtained results is hampered, mainly due to the single-arm trial design.

Results

Population and treatment period

The study included a total of 86 patients i.e. 53 % of the pre-planned study population. Although the study was designed to evaluate the long-term safety (48 weeks), most patients prematurely elected to discontinue their participation because of the commercial availability of the drug. A total of 10 patients prematurely stopped because they were included in another Vertex study. One subject stopped prematurely due to treatment-emergent AEs (elevated transaminases).

None of the patients completed the study, and the actual median study treatment was 22 weeks. The mean age of the study population was 25.3 years, with 27 patients aged 12-18 years upon entry of the respective parent study.

Safety results

Most patients (70.9%) experienced at least 1 adverse event (AE). Most AEs were of mild intensity and resembled adverse events correlated to signs and symptoms of CF disease and the side effects of the triple combination. The frequency of most of AE-events and abnormal lab values were in line with previous reports, including the open label extension study 117 (EMEA/H/C/00529/P46/010).

During the study no new safety events emerged. However, one subject needed to discontinue treatment because of an SAE of elevated AST/ALT > 8 ULN. These LFT elevations were considered to be related to treatment, which was confirmed with a liver biopsy. These observations led to a recommendation to provide a stronger warning about the risk of drug-induced elevated transaminases, which resulted in an update of sections 4.2, 4.4 and 4.8 of the SmPC.

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 (see also procedure EMEA/H/C/005269/P46/009 and EMEA/H/C/005269/P46/010).

Conclusion

This single arm, open-label study provided additional long-term safety with a median duration of 22 weeks for Kaftrio in the treatment of heterozygotic F508/MF subjects with CF.

The currently provided data show 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, however, 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. The planned number for inclusion was n=160, with an actual inclusion of 86 patients i.e. 53 % of the planned population. This raises the following concerns:

a) Please clarify, why not all patients rolled over from the parent study to this observation study and/or why the inclusion was prematurely stopped

b) The applicant is asked to explain why the study was prematurely ended as none of the participants completed the study.

2. It is also noted that most patients did not complete the study due to commercial drug availability. However, this was not a stopping criterium in the study. Please clarify.

3. The study included adults and adolescents from the parent study VX19-445-117 and VX20-445-126.

a) Please indicate the number of patients aged 12-18 years included in this study

b) Please indicate how many patients were recruited form study VX 117 and how many from study VX 126

4. Review of the narratives (shows that this subject experienced the drug related ALT/AST related SAE with ALT and AST elevation up to ≥ 8ULN. This event is described as an event of "mild intensity", but the Rapporteur considers that the severity should be changed to "severe".

a) The applicant is asked to adjust the severity of this event.

b) Please also indicate if the treatment was permanently stopped, or if Kaftrio was re-introduced because of the commercial availability of the drug. If a rechallenge has occurred, please describe the results of the rechallenge.

c) 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 the 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.

d) 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 the 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.

5. The applicant is asked to indicate if the LFT events are considered related or unrelated, and/or if they leaded to treatment discontinuation or treatment interruption, to align with the previously reported data in sections Drug related medication / SAE / Discontinuation / interruption etc.
6. Please provide the total number of events blood bilirubin cases being at least possibly related to medication and the associated severity.
7. Two subjects had a drug related event of CK increased. Please indicate the severity of the event.
8. Please explain why not all patients underwent an ophthalmologic examination upon discontinuation of the trial

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

MAH responses to Request for supplementary information

Question 1

The planned number for inclusion was n=160, with an actual inclusion of 86 patients i.e. 53 % of the planned population. This raises the following concerns:

a) Please clarify, why not all patients rolled over from the parent study to this observation study and/or why the inclusion was prematurely stopped

b) The applicant is asked to explain why the study was prematurely ended as none of the participants completed the study.

Summary of the Applicant's Response

a) Enrollment in Study 121 was lower than the pre-specified number due to subjects who elected not to participate in Study 121. As these subjects completed the parent studies, reasons for not continuing to the separate open-label extension study were not captured in the parent study databases.

- Of the 66 subjects who completed treatment in Study 117, 38 subjects elected not to participate in rollover Study 121.
- Of the 79 subjects who completed treatment in Study 126, 26 subjects elected not to participate in rollover Study 121.

b) Per protocol, end of study was defined as the last scheduled visit (or scheduled contact) of the last subject. As all subjects who participated in Study 121 elected to discontinue treatment and the study (either due to commercial drug availability or to participate in another qualified Vertex study [Study 121 CSR/Listing 16.2.1.1]), the study completed before any subject completed treatment.

Assessment of the Applicant's Response

a) The Applicant provided the numbers of subjects who rolled over from the parent studies and indicated that inclusion was lower because not all subjects of the parent studies elected to continue to the separate open-label study. Reasons for this were not captured. It is noted that a total of 145 subjects completed either one of the parent studies, indicating that the planned number of n=160 was a very optimistic number for inclusion to start with.

b) According to the Applicant's response, all subjects elected to discontinue treatment and thus participation in the study. Whether that was on their own account or on account of the Applicant or Investigator was not specified. It can be concluded that the reason for prematurely ending the study

was that all subjects who were eligible to participate in the study, either decided not to participate or, in case they had decided to participate, elected to discontinue participation in the study.

Conclusion: issue resolved.

Question 2

It is also noted that most patients did not complete the study due to commercial drug availability. However, this was not a stopping criterium in the study. Please clarify.

Summary of the Applicant's Response

As specified in Study 121 Protocol v2.0 Section 9.9, "Subjects may withdraw from the study at any time at their own request or the request of the subject's parent or legal guardian." 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

According to the Applicant's response, in every case that a subject did not complete the study due to commercial drug availability, it was the subject's or subject's caregiver's decision. The stopping criterion was thus primarily withdrawal at their own (or parent's or legal guardian's) request rather than commercial drug availability.

Conclusion: issue resolved.

Question 3

The study included adults and adolescents from the parent study VX19-445-117 and VX20-445-126.

a) Please indicate the number of patients aged 12-18 years included in this study

b) Please indicate how many patients were recruited from study VX 117 and how many from study VX 126

Summary of the Applicant's Response

The number of adult and adolescent subjects enrolled from parent Studies 117 and 126 are presented in Table 5.

Table 5 Study 121 Enrolment by Parent Study and Age (Safety Set)

	Total N	Adult (≥18 Years of Age) n	Adolescent (12 to <18 Years of Age) n
Subjects enrolled in Study 121	86	59	27
Subjects from Study 117	31	21	10
Subjects from Study 126	55	38	17

Source: Study 121/Adhoc Table 1
n: size of subsample; N: total sample size
Notes: Age category is presented from parent study baseline, which was defined as the most non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period of parent studies (Studies 117 and 126).

Assessment of the Applicant's Response

The Applicant provided the requested data. The study included 27 subjects aged 12-18 years (31%). 31 subjects (36%), of whom 10 aged 12-18 years, were recruited from parent study VX19-445-117.

55 subjects (64%), of whom 17 aged 12-18 years, were recruited from parent study VX20-445-126. The overview has been updated accordingly.

Conclusion: issue resolved.

Question 4

Review of the narratives (One Subject) shows that this subject experienced the drug related ALT/AST related SAE with ALT and AST elevation up to ≥ 8ULN. This event is described as an event of "mild intensity", but the Rapporteur considers that the severity should be changed to "severe".

a) The applicant is asked to adjust the severity of this event.

b) Please also indicate if the treatment was permanently stopped, or if Kaftrio was re-introduced because of the commercial availability of the drug. If a rechallenge has occurred, please describe the results of the rechallenge.

c) 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 the 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.

d) 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 the 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

a) As defined in Study 121 Protocol v2.0 Section 13.1.1.4, adverse event (AE) severity was assessed by the investigator in accordance with Common Terminology Criteria for Adverse Events (CTCAE) guidance (e.g., Grade 1 [mild] severity is described as "mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated"). Vertex cannot adjust the severity of the AEs of alanine transaminase (ALT) increased and aspartate transaminase (AST) increased for one Subject as this conflicts with GCP guidelines for clinical trial execution.

b) Following the AEs of ALT increased and AST increased, this subject discontinued elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) treatment in Study 121. There was no rechallenge during study participation with ELX/TEZ/IVA following the AEs of ALT increased and AST increased. The subject received the last dose of study drug on 31 July 2022. On 19 September 2022, the subject discontinued Study 121.

c) and d) Vertex agrees to update the Summary of Product Characteristics (SmPC) to more clearly address the risk of elevated transaminases as well as treatment discontinuations due to elevated transaminases; proposed changes are included in the attached SmPC.

Assessment of the Applicant's Response

a) The investigator assigned the event as "mild" referring Common Terminology Criteria for Adverse Events (CTCAE) to assess the AEs. However, by using the same classification system, we consider that the severity might be under estimated. Considering that the subject received an AE induced intervention (liver biopsy), the event should have at least been classified as moderate. In addition, the liver biopsy showed sign of drug-induced liver injury. A drug-induced liver injury can be potential life

threatening if treatment is continued. Therefore, the classification as "severe" would align with the CTCAE classification.

It is acknowledged that the Applicant cannot adjust the severity of the AEs as determined by the investigator. However, considering that the event was reported as serious, it could have been considered that the investigator might have underestimated the severity of this event.

b) The Applicant states that the study drug was not reintroduced to this subject during the study. During the study, no rechallenge test occurred.

c) And d) Applicant proposed changes to the SmPC that address the risk of elevated transaminases and events of elevated transaminases in clinical studies. With these changes, the Applicant provides a clearer/stronger warning about the risk of drug induced elevated transaminases and the occurrence of this AE in clinical trials.

Conclusion: issue resolved.

Question 5

The applicant is asked to indicate if the LFT events are considered related or unrelated, and/or if they leaded to treatment discontinuation or treatment interruption, to align with the previously reported data in sections Drug related medication / SAE / Discontinuation / interruption etc.

Summary of the Applicant's Response

One subject (discontinued treatment due to elevated transaminase events and another subject interrupted study drug due to elevated transaminase events. Outcome and the investigator's assessment of relatedness for all treatment-emergent elevated transaminase events are presented in Table 6.

Table 6 Elevated Transaminase Events During the TE Period (All Subjects Set)

Subject	PT	Action Taken ELX/TEZ/IVA; IVA	Relationship to Study Drug
[redacted]	ALT increased	Drug interrupted; Drug interrupted	Unlikely related
	AST increased	Drug interrupted; Drug interrupted	Unlikely related
[redacted]	ALT increased	Dose not changed; Dose not changed	Related
	AST increased	Dose not changed; Dose not changed	Related
[redacted]	ALT increased	Drug withdrawn; Drug withdrawn	Related
	AST increased	Drug withdrawn; Drug withdrawn	Related

Source: Listing 16.2.7.2
ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; IVA: ivacaftor; PT: Preferred Term; TE: treatment-emergent; TEZ: tezacaftor
Notes: Adverse events were coded using MedDRA version 25.1.

Assessment of the Applicant's Response

The Applicant provided an additional overview of the PT elevated transaminase events for two subjects, one of which led to treatment interruption and one which led to treatment discontinuation.

Elevated transaminase levels are common in patients with CF. Therefore, elevated transaminase levels are not necessarily related to the study drug.

The Rapporteur expected that the reported drug-related AST/ALT leading to an SAE of the first above subject (see question 4) would be of at least moderate to severe severity, also considering that it led to discontinuation of the drug treatment. However, in the initial study report, the reported case of increase ALT/AST was considered not related to treatment, although it led to treatment interruptions.

The Applicant clarified in response to question 4, why the treatment related SAE of AST/ALT increased experience by this subject was considered of mild intensity. In response to question 5, the Applicant provided an additional overview of the related and unlikely PT elevated transaminase events for three subjects. As shown by this table, the event of moderate intensity was experienced by another subject).

A complete overview of the PT ALT/AST increased is provided in listing 16.2.7.2: a summary is provided in the table below :

Subject	PT	Severity	Action taken		Relationship to study drug
[redacted]	ALT increased	Mild	Dose not changed	Dose not changed	Not related
[redacted]	ALT increased	Moderate	Drug interrupted	Drug interrupted	Unlikely related
	AST increased	Severe	Drug interrupted	Drug interrupted	Unlikely related
[redacted]	ALT increased	Mild	Dose not changed	Dose not changed	Possibly related
[redacted]	ALT increased	Mild	Dose not changed	Dose not changed	Related
	AST increased	Mild	Dose not changed	Dose not changed	Related
[redacted]	ALT increased	Mild	Drug withdrawn	Drug withdrawn	Related
	AST increased	Mild	Drug withdrawn	Drug withdrawn	Related

Table made by assessor based on listing 16.2.7.2.

Overall, the Rapporteurs considers that 3 patients experienced a treatment related of increased AST/ALT, with all events being reported as "mild" by the investigator. Four events were considered as related and one additional event is considered as possibly related.

As already mentioned in response to question 4, in one subject the severity might potentially have been underrated. As stated in question 4, one subject experienced an SAE of AST/ALT elevations of >8 ULN. This event was considered to be related to treatment, which was confirmed with a liver biopsy. These observations led to a recommendation to provide a stronger warning about the risk of drug-induced elevated transaminases, which resulted in an proposed update of sections 4.2, 4.4 and 4.8 of the SmPC.

Conclusion: issue resolved.

Question 6

Please provide the total number of events blood bilirubin cases being at least possibly related to medication and the associated severity.

Summary of the Applicant's Response

There were 3 treatment-emergent events related to blood bilirubin that were assessed by the investigator as possibly related to study drug: 1 subject had an AE of hyperbilirubinemia and 1 subject had separate AEs of blood bilirubin increased and blood bilirubin unconjugated increased. All 3 events were assessed by the investigator as mild in severity.

There were no events related to blood bilirubin that were considered related to study drug.

Assessment of the Applicant's Response

In 22 subjects elevated total bilirubin levels > ULN were measured and in 17 subjects elevated direct bilirubin levels were measured.

Not all cases of elevated total bilirubin will be recorded as adverse event. According to listing 16.2.7.1 a total of n=5 patients experienced a possibly related event of elevated bilirubin considered of mild intensity by the investigator. These events did not lead to a dose modification.

Conclusion: issue resolved.

Question 7

Two subjects had a drug related event of CK increased. Please indicate the severity of the event.

Summary of the Applicant's Response

The 2 subjects with an AE of blood creatine phosphokinase increased that was assessed by the investigator as possibly related to study drug had events that were mild or moderate in severity, summarized below:

- Subject had an AE of blood creatine phosphokinase increased that was mild in severity; study drug dosing was not changed.
- Subject had an AE of blood creatine phosphokinase increased that was moderate in severity; study drug dosing was not changed.

Assessment of the Applicant's Response

The Applicant provided the requested information. One of the two events was considered mild and the other moderate in severity. In both cases, study drug dosing was not changed.

Conclusion: issue resolved.

Question 8

Please explain why not all patients underwent an ophthalmologic examination upon discontinuation of the trial

Summary of the Applicant's Response

Per Study 121 Protocol v2.0 Section 11.2.7, ophthalmologic examinations (OEs) were planned to be conducted only for the 27 subjects who were <18 years of age on the date of informed consent in a parent study.

- 9 subjects had OEs conducted and included in the electronic data capture (EDC).
- 3 subjects discontinued Study 121 to participate in another qualified Vertex study and had an OE conducted as part of the Screening Visit in that study; none of the subjects had an AE of cataract.
- 2 subjects, who had previously participated in Study 445-117 (Study 117), had an OE as part of their Study 117 Week 48 Visit. These OEs were within the window of time that precluded the requirement of another OE in Study 121, per Study 121 Protocol v2.0 Section 11.2.7.
- 13 subjects had an OE conducted at study discontinuation that were not entered in the EDC. Based on review of the source data and communication with the site investigators, all OEs were conducted per protocol and there were no treatment-emergent AEs of cataracts.

Assessment of the Applicant's Response

All 27 subjects aged 12-18 years underwent an OE, either at discontinuation of the study or within a window of time that precluded the requirement of another OE. For 18 subjects, this was not properly recorded in the study report and additional explanation was provided.

Conclusion: issue resolved.