25 February 2021
EMA/278069/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Orkambi

lumacaftor / ivacaftor

Procedure no: EMEA/H/C/003954/P46/016.1

Note

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
ETT	Early Termination of Treatment
IPD	important protocol deviation
IRB	institutional review board
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
LCI	lung clearance index
LCI2.5	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LCI5.0	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value
LFT	liver function test
LLOQ	lower limit of quantification
LMM	linear mixed model
LS	least squares
LUM	lumacaftor
L/I	lumacaftor/ivacaftor
max	maximum value
MBW	multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
N	total sample size
n	size of subsample
NE	not estimable
NHLBI	National Heart, Lung, and Blood Institute
OE	ophthalmological examination
P	placebo
P	probability
PCS	potentially clinically significant

PD	pharmacodynamic, pharmacodynamics
PDCO	European Medicines Agency Pediatric Committee
PEx	pulmonary exacerbation
PK	pharmacokinetic, pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
PY	patient-year
q12h	every 12 hours
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next; use R-R if using with "intervals", i.e., "R-R interval"
ROS	Rollover Set
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SI	SI units (International System of Units)
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
US	United States
USA	United States of America
UTE	ultrashort echo time
WHO-DD	World Health Organization-Drug Dictionary

Introduction

On 29/09/2020, the MAH submitted a completed paediatric study for Orkambi [**VX15-809-110 (Treatment Period 2)**], in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study VX15-809-110 (Study 110) was a Phase 3, open label, multicenter, rollover study in subjects aged 6 years and older with cystic fibrosis (CF), who were homozygous for F508del-CFTR, and who participated in parent Study VX14-809-109 or Study VX13-809-011B. Study 110 consisted of 2 Treatment Periods.

Treatment Period 1 was a 96-week study designed to evaluate the long-term safety and tolerability of LUM/IVA treatment for 96 weeks in subjects aged 6 years and older with cystic fibrosis (CF), homozygous for F508del. Efficacy was evaluated as a secondary objective. The results of treatment Period 1 **[Study 110 Treatment Period 1 CSR (dated 25 February 2019)]** have been previously submitted under Article 16 of Commission Regulation (EC) No. 1234/2008 as a Type II variation (EMEA/H/C/003954/II/0049, CHMP Opinion 09 July 2020).

Treatment Period 2 was optional for subjects enrolled in France who completed LUM/IVA treatment in Treatment Period 1 and were aged 6 through 11 years at the time of entry into Treatment Period 2. LUM/IVA was to be administered for up to approximately 168 weeks of additional LUM/IVA treatment, or until LUM/IVA was commercially available for the eligible subjects.

The **Study 110 Final CSR (dated 24 August 2020)**, submitted by the MAH within this procedure, includes the final results from both Treatment Periods 1 and 2. The MAH states that because Treatment Period 1 has already been assessed by CHMP as a Type II variation (EMEA/H/C/003954/II/0049), only Treatment Period 2 results are being submitted under Article 46 and are discussed further below.

A short critical expert overview has also been provided.

CHMP comment

The MAH should clarify if, apart from the results of Treatment Period 2, there are other differences between **Study 110 Treatment Period 1 CSR (dated 25 February 2019)**, previously submitted within variation EMEA/H/C/003954/II/0049, and **Study 110 Final CSR (dated 24 August 2020)**, submitted by the MAH within this procedure. Differences between the two CSR should be highlighted and adequately discussed **(OC).**

1. Scientific discussion

1.1. Information on the development program

Only the results of Treatment Period 2 of study VX15-809-110 (Study 110) are being submitted under Article 46 and are discussed further below.

The MAH has submitted the results of treatment period 2 of study VX15-809-110 (Study 110), which included paediatric patients, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

1.2. Information on the pharmaceutical formulation used in the study

Formulation and Composition: 100-mg LUM/125-mg IVA fixed dose tablets

Dose Regimen: LUM 200 mg/IVA 250 mg q12h

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

Study: VX15-809-110 (Treatment Period 2)

Study Initiation (Treatment Period 2): 21 March 2018 (date first eligible subject signed the informed consent/assent form)

Study Completion (Treatment Period 2): 24 April 2020 (date last subject completed the Safety Follow-up Visit)

Treatment Period 2 was conducted at 3 sites in France.

Treatment Period 2 was optional for subjects enrolled in France who completed LUM/IVA treatment in Treatment Period 1 and were aged 6 through 11 years at the time of entry into Treatment Period 2. LUM/IVA was to be administered for up to approximately 168 weeks of additional LUM/IVA treatment in Treatment Period 2 or until LUM/IVA was commercially available for the eligible subjects. All 10 subjects enrolled in Treatment Period 2 discontinued treatment when commercial drug became available for children 6 through 11 years of age in France. Thus, the maximum treatment duration in Treatment Period 2 was up to approximately 89 weeks of additional LUM/IVA treatment. Treatment duration of LUM/IVA ranged from 80 to 624 days in Treatment Period 2).

The **Study 110 Final CSR (dated 24 August 2020)**, submitted by the MAH within this procedure, includes the final results from both Treatment Periods 1 and 2. The MAH states that because Treatment Period 1 has already been assessed by the EMA as a Type II variation (EMEA/H/C/003954/II/0049), only Treatment Period 2 results are being submitted under Article 46 and are discussed further below.

Study 110 Treatment Period 1 CSR (dated 25 February 2019) was previously submitted to the EMA under Article 16 of Commission Regulation (EC) No. 1234/2008 as a Type II variation (EMEA/H/C/003954/II/0049).

1.3.2. Clinical study

Description

Methods

Objective(s)

Primary Objective: There was no primary objective for Treatment Period 2.

Secondary Objective: To evaluate the long-term safety of LUM/IVA for subjects in Treatment Cohort Period 2.

Study design

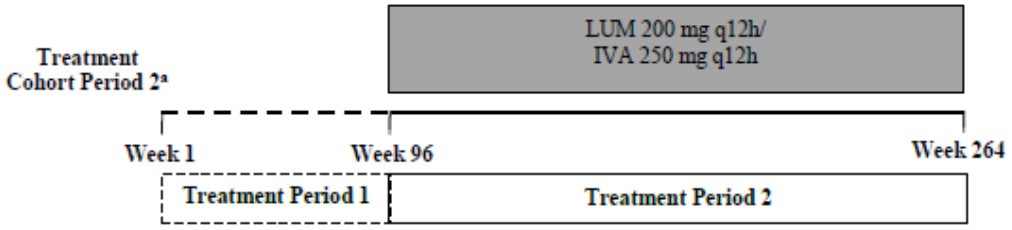
Figure 1 shows the study design for Treatment Period 2.

Treatment Period 2 included only a Treatment Cohort (referred to as Treatment Cohort Period 2) and was optional for subjects enrolled in France who completed Treatment Cohort Period 1 and who were aged 6 through 11 years at the time of entry into Treatment Period 2. LUM/IVA was to be administered for up to approximately 168 additional weeks in Treatment Period 2 or until LUM/IVA was commercially available for the eligible subjects.

In Treatment Period 2, safety assessments included vital signs, physical examinations, ophthalmologic examinations, serum chemistry for liver function test (LFT) parameters, and monitoring of adverse events (AEs) and serious AEs (SAEs) at longer intervals than assessed in Treatment Period 1.

Efficacy was not evaluated in Treatment Period 2.

Figure 1 Study Design for Study 110 Treatment Period 2



Source: Adapted from Study 110 Final CSR/Figure 9-1
IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours.
[a] Treatment Cohort Period 2 was optional for subjects at sites in France who completed Treatment Cohort Period 1 and who were aged 6 through 11 years at the time of entry into Treatment Period 2. Week 96 of Treatment Period 1 was the start of Treatment Period 2.

Table 9-5 Study VX15-809-110: Optional Treatment Cohort Period 2

Event/Assessment[a]	Treatment Period[b] Weeks 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264 (± 1 week)	Early Treatment Termination Visit[c]
Clinic visit	X	X
Urine β-hCG (all female subjects who have undergone menarche from the beginning of Treatment Cohort Period 2 or at any point through the end of study or the ETT Visit [Section 9.5.7.2])	X	X
Vital signs[d]	Weeks 144, 192, 240, and 264 only	X
Full physical examination[e]	Weeks 144, 192, 240, and 264 only	X
Ophthalmologic examination[f]	Week 192 and 264 only	X
Serum chemistry; LFTs only (ALT, AST, GGT, ALP, and total bilirubin)	Weeks 144, 192, 240, and 264 only	X
Study drug dosing[g]	**LUM 200 mg q12h/IVA 250 mg q12h**	
Study drug count	X	X
AEs and SAEs[h]	**Continuous, from signing of ICF (and assent form, if applicable) through end of study**	

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; β-hCG: beta-human chorionic gonadotropin; ETT: early treatment termination; GGT: gamma-glutamyl transferase; GPS: Global Patient Safety; ICF: informed consent form; IVA: ivacaftor; LFT: liver function test; LUM: lumacaftor; OE: ophthalmological examination; q12h: every 12 hours; SAE: serious adverse event.

a All assessments were performed before study drug dosing unless noted otherwise (Section 9.5.2). Data from unscheduled assessments could be evaluated by Vertex.
b Week 96 was the first visit for subjects 6 through 11 years of age who completed Treatment Cohort Period 1 and elected to enter Treatment Cohort Period 2 (Table 9-4).
c Subjects who prematurely discontinued study drug treatment were asked to complete the ETT Visit. The ETT Visit should be scheduled as soon as possible after the subject decided to terminate study treatment.
d Vital signs were collected before study drug dosing after the subject had been at rest (seated or supine) for at least 5 minutes (Section 9.5.7.4).
e Symptom-directed physical examinations occurred at any time during the study if triggered by AEs or if deemed necessary by the investigator or health care provider (Section 9.5.7.4).
f An OE was conducted by a licensed ophthalmologist or optometrist (Section 9.5.7.6). Subjects with documentation of bilateral lens removal did not need the OE. If a cataract or lens opacity was identified and determined to be clinically significant by a licensed ophthalmologist or optometrist at the Week 96 (Treatment Cohort Period 1) examination (also see Footnote b), the subject was notified. After discussion with the site principal investigator, the subject could elect to continue or discontinue the study. If the subject discontinued study drug, they completed the ETT Visit (Section 9.3.5). If the subject continued, more frequent ophthalmologic monitoring was considered.
g The study drug was administered q12h (± 2 hours) within 30 minutes of consuming fat-containing food (Section 9.4.1). On days of scheduled visits, the dose of study drug was administered at the site after predose assessments had been completed. The last dose of study drug was administered at the Week 264 Visit.
h SAEs that occurred after the ETT Visit and were considered related to study drug(s) were reported to Vertex GPS **within 24 hours** as described in Appendix 16.1.1/Protocol Version 3.1 FR/Section 13.1.2.2.

Study population /Sample size

Eligibility Criteria

Treatment Period 2 was conducted only in France and was optional for subjects who completed Treatment Period 1. The key inclusion criterion for subjects entering Treatment Cohort Period 2 was:

• Completed dosing in Treatment Cohort Period 1 and were within the age range of 6 through 11 years.

NOTE: Subjects 6 through 11 years of age who discontinued Treatment Cohort Period 2 could not re-enroll in Study 110.

Exclusion Criteria (same exclusion criteria for Treatment Cohorts 1 and 2)

Subjects who met any of the following exclusion criteria were not eligible:

1. History of any comorbidity or laboratory abnormality that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to the subject (e.g., cirrhosis with portal hypertension).

2. Pregnant and nursing females. Females of childbearing potential must have had a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of study drug.

3. Sexually active subjects of reproductive potential who were not willing to follow the contraception requirements outlined in Protocol Version 2.0 and Protocol Version 3.1.

4. History of drug intolerance in the previous (parent) study that would have posed an additional risk to the subject in the opinion of the investigator, and which should have been discussed with the Vertex medical monitor. Examples of subjects who may not have been eligible for Treatment Cohort Periods 1 or 2 included (but were not limited to) the following:

• Subjects with a history of allergy or hypersensitivity to the study drug

• Liver function test (LFT) abnormality during study drug treatment in the previous (parent) study (Study 109 or Study 011B) or Treatment Cohort Period 1 for which a clear cause was not identified:

o Abnormal liver function defined as any 2 or more of the following:

a. ≥3 × upper limit of normal (ULN) aspartate transaminase (AST)

b. ≥3 × ULN alanine transaminase (ALT)

c. ≥3 × ULN gamma-glutamyl transferase (GGT)

d. ≥3 × ULN alkaline phosphatase (ALP)

o ALT or AST >5 × ULN

o Total bilirubin >2 × ULN

o Other LFT abnormalities that would have posed an additional risk to the subject in the opinion of the investigator or Vertex

• Other severe or life-threatening reactions to the study drug in the previous (parent) study

5. History of poor compliance with study drug and/or procedures in the previous (parent) study as deemed by the investigator.

6. Participation in an investigational drug trial (including studies investigating LUM and/or IVA). NOTE: Participation in a non-interventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) was permitted (Treatment Cohort Period 1 only).

Study Restrictions

The medications described in Table 9-1 were prohibited while subjects were receiving LUM/IVA.

A non-exhaustive list of study prohibitions and cautions for food and medication was provided in the Study Reference Manual.

Table 9-1 Study Restrictions

Restricted Medication/Food[a]	Treatment Period
Strong CYP3A inducers	None allowed
Strong CYP3A inhibitors	Use with caution

Note: The use of restricted medication in subjects with a medical need was addressed on a case-by-case basis with the medical monitor or authorized designee.

[a] See Section 9.3.4 for guidance for concomitant medications.

Treatments

LUM/IVA tablets were administered orally every 12 hours (q12h).

In Treatment Period 2, subjects aged 6 through 11 years received LUM 200 mg/IVA 250 mg (2 × LUM 100-mg/IVA 125-mg tablet).

Outcomes/endpoints

Safety data: For Treatment Cohort Period 2, the analysis of safety data was limited to AEs, SAEs, LFTs, vital signs, and OEs.

Clinical Laboratory: The following analyses for the LFT parameters of ALT, AST, ALP, and total bilirubin were conducted:

• The number and percentage of subjects meeting the defined threshold criteria (SAP Version 1.0) during the Treatment-emergent Period of Treatment Cohort Period 2 were summarized.

• A listing for subjects with all LFT results during the Treatment-emergent Period of Treatment Cohort Period 2 was presented. The listing included all parameters of the LFT assessment at all visits.

Results of the urine pregnancy tests were listed in an individual subject data listing.

Vital sign parameters and Ophthalmological Examinations (OE) were presented as a data listing only.

Statistical Methods

For Treatment Cohort Period 2 subjects, safety analyses were based on the treatment-emergent period, which started from the Study 110 Week 96 dose date +1 or Week 96 visit date +1, whichever occurred later; up to 28 days (inclusive) after the last dose of this dosing period, or the last available date in Study 110 Treatment Cohort Period 2, whichever occurred first.

For Treatment Cohort Period 2, all summaries included all subjects enrolled in that cohort.

For Treatment Cohort Period 2, AEs were classified as TEAEs or post-treatment AEs.

• TEAE: any AE that increased in severity or that was newly developed in the treatment-emergent period of Treatment Cohort Period 2.

• Post-treatment AE: any AE that increased in severity or that was newly developed in the post-treatment period of Treatment Cohort Period 2.

AEs with missing or partial start dates were classified as TEAEs if there was no clear evidence that the AEs started before or after study treatment. Details regarding handling rules of missing dates are included in SAP Version 1.0.

AE summary tables were presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts, percentages (i.e., number and percentage of subjects with 1 or more events), and exposure-adjusted number of events (i.e., number of events per 100 patient-years [100PY]). When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same AE or a continuing AE were counted once, and only the maximum severity level was presented in the severity summaries, and the worst/highest relationship level in the relationship summaries. Exposure-adjusted number of events summarized the number of events per 100PY for AE-related safety data. Note: 1 patient with 48 weeks of exposure duration was defined as 1 patient-year.

Results of safety assessments for Treatment Cohort Period 2 were summarized for all enrolled subjects using descriptive statistics; no formal statistical testing was performed.

CHMP comment

AEs for Treatment Period 2 have been presented only as number and percentage of subjects with an event. When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same AE within a category was counted only once in that category.

Exposure-adjusted number of events (i.e., number of events per 100 patient-years [100PY]) have not been presented for Treatment Period 2.

However, given that only 10 patients have been enrolled in Treatment Period 2, the issue is not further pursued.

COVID-19

Three subjects from 1 site in Treatment Period 2 were impacted by the COVID-19 pandemic. Safety measures were implemented to provide subjects the opportunity to continue participation in the study while ensuring their safety by minimizing the risk to COVID-19 exposure through travel.

These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to study integrity.

A summary of these measures pertinent to Study 110 Treatment Cohort Period 2 are summarized in Protocol Addendum 1.

• Subjects were contacted by site personnel by telephone/video call to complete the remaining scheduled visits (i.e., the ETT visit). During this telephone/video call(s), the safety and tolerability of LUM/IVA was evaluated to ensure subject safety. These assessments included a review of AEs, medications, and study drug administration.

• Blood samples for safety assessments were collected and analyzed at local laboratories. Specifically, an LFT panel was performed, including ALT, AST, GGT, ALP, and total bilirubin.

Results

Recruitment/ Number analysed

Of the 240 subjects in Treatment Cohort Period 1, 13 subjects were enrolled at sites in France. Ten subjects were eligible for Treatment Cohort Period 2; all 10 enrolled and received at least 1 dose of LUM/IVA during Treatment Period 2. All 10 subjects discontinued treatment when commercial drug became available for children 6 through 11 years of age in France.

The treatment duration of LUM/IVA ranged from 80 to 624 days for subjects in Treatment Cohort Period 2.

No subjects completed treatment or the study in Treatment Cohort Period 2; all 10 (100.0%) subjects discontinued treatment because commercial drug became available in France.

CHMP comment

During Treatment Period 2, LUM/IVA was to be administered for up to approximately 168 weeks of additional LUM/IVA treatment or until LUM/IVA was commercially available for the eligible subjects. All 10 subjects enrolled in Treatment Period 2 discontinued treatment early, when commercial drug became available for children 6 through 11 years of age in France. Thus, the maximum treatment duration in Treatment Period 2 was up to approximately 89 weeks of additional LUM/IVA treatment. Treatment duration of LUM/IVA in Treatment Period 2 ranged from 80 to 624 days (from less than 3

months to slightly less than 2 years). The MAH should provide mean and median treatment duration in Treatment Period 2, for the 10 patients enrolled in Treatment Period 2 (**OC**).

Baseline data

Nine out of 10 subjects were White (90.0%) and not Hispanic or Latino (90.0%). Half of the subjects were male (50.0%). The mean age at parent study baseline was 7.6 years (SD: 0.84; range 6 to 9 years).

The most common concomitant medications (>50% of subjects) taken during Treatment Period 2 were pancreatin, cholecalciferol, dornase alfa, sodium chloride, amoxicillin/clavulanic acid, tobramycin, and tocopheryl acetate.

Table 10-8 Baseline Characteristics Based on Start of Studies 109/011B (All Enrolled Subjects for Treatment Cohort Period 2)

Characteristic	Overall N = 10
Weight (kg)	
n	10
Mean (SD)	26.2 (5.4)
SE	1.7
Median	23.8
Min, max	21.5, 39.0
Weight *z*-score[a]	
n	10
Mean (SD)	-0.22 (0.84)
SE	0.26
Median	-0.26
Min, max	-1.32, 1.42
Height (cm)	
n	10
Mean (SD)	128.7 (4.7)
SE	1.5
Median	127.9
Min, max	121.5, 137.5
Height *z*-score[a]	
n	10
Mean (SD)	0.03 (0.62)
SE	0.20
Median	-0.02
Min, max	-0.82, 1.30
BMI (kg/m^2)	
n	10
Mean (SD)	15.71 (2.28)
SE	0.72
Median	15.37
Min, max	13.12, 20.63
BMI *z*-score[a]	
n	10
Mean (SD)	-0.48 (1.22)
SE	0.39
Median	-0.41
Min, max	-2.43, 1.43
Sweat chloride (mmol/L)	
n	10
Mean (SD)	102.7 (10.2)
SE	3.2
Median	104.6
Min, max	87.5, 119.0

Table 10-8 Baseline Characteristics Based on Start of Studies 109/011B (All Enrolled Subjects for Treatment Cohort Period 2)

Characteristic	Overall N = 10
$LCI_{2.5}$	
n	10
Mean (SD)	9.59 (2.13)
SE	0.67
Median	9.10
Min, max	7.16, 13.87
$ppFEV_1$ (percentage points)	
n	10
Mean (SD)	95.5 (9.2)
SE	2.9
Median	94.8
Min, max	77.9, 110.4
$ppFEV_1$ category	
<90	3 (30.0)
≥90	7 (70.0)

Source: Table 14.1.4a2

BMI: body mass index; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; N: total sample size; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Note: Baseline for sweat chloride was defined as the average of the measurements at screening and on Day 1 predose in Studies 109/011B; baseline for other variables was defined as the most recent measurement before the first dose of study drug in Studies 109/011B.

[a] The *z*-scores were calculated by using the National Center for Health Statistics growth charts.

Measurements of Treatment Compliance: Study drug compliance was 100% for each individual subject during Treatment Cohort Period 2

Efficacy results

Not applicable. Efficacy was not evaluated in Treatment Period 2.

Safety results

• A total of 9 subjects had at least 1 AE.

• All 9 subjects had AEs that were mild or moderate in severity, and none had AEs that were considered related or possibly related to study drug.

One (10.0%) subject had 1 AE that was considered unlikely related to study drug (SOC: Nervous system disorders/ PT: Headache, mild in severity, dose not changed, treatment required, outcome: not recovered/ not resolved).

• There were no deaths.

• No subject had an SAE, AE leading to treatment discontinuation, or AE leading to treatment interruption.

• No subject had ALT or AST >3 × Upper Limit of Normal (ULN), ALP >1.5 × ULN, or total bilirubin >1.5 × ULN. No subject had an AE related to elevated transaminases

• No clinically meaningful adverse changes or trends were observed for laboratory or vital sign measurements.

For 17/58 (29%) of the TEAEs, the outcome was reported as not recovered/ not resolved. Apart from one event of mild Headache (reported as unlikely related), all the other events were reported as not related and the dose was not changed following the occurrence of the event. Twelve of these events were mild [PTs: headache, gastritis, cough (n=2), rhinitis, nasopharyngitis, hepatomegaly, epistaxis, dyspepsia, constipation, rhinitis allergic, wheezing) and five were moderate in intensity (PTs: abdominal pain, glucose tolerance impaired, bacterial disease carrier, bronchiectasis, bronchitis).

Table 12-9 AEs With an Incidence of At least 20% (n=2) of Subjects by PT (All Enrolled Subjects for Treatment Cohort Period 2)

Preferred Term	Overall N = 10 n (%)
Any AEs	9 (90.0)
Rhinitis	6 (60.0)
Infective PEx of CF	4 (40.0)
Nasopharyngitis	3 (30.0)
Bacterial disease carrier	2 (20.0)
Bronchitis	2 (20.0)
Cough	2 (20.0)
Epistaxis	2 (20.0)

Source: Table 14.3.1.2a2

AE: adverse event; CF: cystic fibrosis; N: total sample size; n: size of subsample; PEx: pulmonary exacerbation; PT: preferred term

Notes: MedDRA Version 22.1 was used. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. Percentages were calculated based on the number of subjects enrolled in the Study 110 Treatment Cohort Period 2.

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Table 14.3.1.2a2
TEAEs by System Organ Class and Preferred Term - Treatment Cohort Period 2
All Enrolled Subjects for Treatment Cohort Period 2

System Organ Class Preferred Term	Overall N = 10 n (%)
Any TEAEs	9 (90.0)
Infections and infestations	8 (80.0)
Rhinitis	6 (60.0)
Infective pulmonary exacerbation of cystic fibrosis	4 (40.0)
Nasopharyngitis	3 (30.0)
Bacterial disease carrier	2 (20.0)
Bronchitis	2 (20.0)
Ear infection	1 (10.0)
Gastroenteritis	1 (10.0)
Oral fungal infection	1 (10.0)
Respiratory tract infection bacterial	1 (10.0)
Respiratory, thoracic and mediastinal disorders	5 (50.0)
Cough	2 (20.0)
Epistaxis	2 (20.0)
Bronchiectasis	1 (10.0)
Lower respiratory tract congestion	1 (10.0)
Paranasal sinus hypersecretion	1 (10.0)
Rales	1 (10.0)
Rhinitis allergic	1 (10.0)
Wheezing	1 (10.0)
Gastrointestinal disorders	4 (40.0)
Abdominal pain	1 (10.0)
Constipation	1 (10.0)
Diarrhoea	1 (10.0)

Table 14.3.1.2a2
TEAEs by System Organ Class and Preferred Term - Treatment Cohort Period 2
All Enrolled Subjects for Treatment Cohort Period 2

System Organ Class Preferred Term	Overall N = 10 n (%)
Dyspepsia	1 (10.0)
Gastritis	1 (10.0)
Nausea	1 (10.0)
Investigations	2 (20.0)
Forced expiratory volume decreased	1 (10.0)
Pulmonary imaging procedure abnormal	1 (10.0)
Weight decreased	1 (10.0)
Eye disorders	1 (10.0)
Eyelid oedema	1 (10.0)
General disorders and administration site conditions	1 (10.0)
Pyrexia	1 (10.0)
Hepatobiliary disorders	1 (10.0)
Hepatomegaly	1 (10.0)
Injury, poisoning and procedural complications	1 (10.0)
Ligament sprain	1 (10.0)
Metabolism and nutrition disorders	1 (10.0)
Glucose tolerance impaired	1 (10.0)
Musculoskeletal and connective tissue disorders	1 (10.0)
Arthralgia	1 (10.0)

Table 14.3.1.2a2
TEAEs by System Organ Class and Preferred Term - Treatment Cohort Period 2
All Enrolled Subjects for Treatment Cohort Period 2

System Organ Class Preferred Term	Overall N = 10 n (%)
Nervous system disorders	1 (10.0)
Headache	1 (10.0)

- MedDRA version 22.1.
- N: Number of subjects enrolled in the Study 110 Treatment Cohort Period 2.
- n: number of subjects; TEAE: Treatment-emergent adverse event.
- TEAE starts from the Study 110 Week 96 dose date + 1, or Week 96 visit date +1, whichever occurs later; up to 28 days (inclusive) after the last dose of this dosing period, or the last available date in Study 110 Treatment Cohort Period 2, whichever occurs first.
- A subject with multiple events within a category is counted only once in that category.
- Table is sorted in descending order of the incidence column of Overall by SOC, and in descending order by PT within each SOC.
- Percentages were calculated based on the number of subjects enrolled in the Study 110 Treatment Cohort Period 2.

CHMP comment

Of note, in the Tables reporting AEs by PT, when summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

Thus, the information provided may be misleading. For example the PT of infective PEX of CF are 4 (40%) but PEx occurred more than one time in 2 out of 4 subjects: in two subjects ≥2 PEx event occurred (of note, in one of these subjects, 3 PEx events occurred within 8 months); in a third subject one event of PEx and a further event of Pneumopathy/ Radiological Focus on the left base of the lung occurred.

Weight, Height, and BMI

Weight, height, and BMI data were generally consistent with a growing pediatric population. One subject had an AE of weight decreased that was moderate in severity and considered not related to study drug.

Ophthalmological Examinations

One subject had abnormal lens findings on both eyes at the ETT visit; no lens opacity was reported. Previous OEs for this subject were normal, including visits during Treatment Period 1. All other subjects had normal lens findings in Treatment Cohort Period 2. No subject had an AE related to lens findings.

CHMP comment

The MAH states that one subject, with previous normal Ophthalmological Examinations, had abnormal lens findings on both eyes at the Early Termination of Treatment visit. The MAH should clarify what kind of abnormal findings were reported and provide information on the follow-up of this event i.e. resolved/not **(OC)**.

1.3.3. Discussion on clinical aspects

Study VX15-809-110 (Study 110) was a Phase 3, open label, multicenter, rollover study in subjects aged 6 years and older with cystic fibrosis (CF), who were homozygous for F508del-CFTR, and who participated in parent Study VX14-809-109 or Study VX13-809-011B.

Study 110 consisted of 2 Treatment Periods.

Treatment Period 1 was a 96-week study designed to evaluate the long-term safety and tolerability of LUM/IVA treatment for 96 weeks in subjects aged 6 years and older with cystic fibrosis (CF), homozygous for F508del. Efficacy was evaluated as a secondary objective. Treatment Period 1 results have already been assessed by CHMP through a Type II variation (EMEA/H/C/003954/II/0049).

The MAH states that only Treatment Period 2 results are being submitted under Article 46 and thus only results of Treatment Period 2 are discussed in this AR.

However, given that Study 110 Final CSR (dated 24 August 2020), submitted by the MAH within this procedure, includes the final results from both Treatment Periods 1 and 2, the MAH was requested to clarify if, apart from the results of Treatment Period 2, there were other differences between **Study 110 Treatment Period 1 CSR (dated 25 February 2019)**, previously submitted within variation EMEA/H/C/003954/II/0049, and **Study 110 Final CSR (dated 24 August 2020)**, submitted by the MAH within this procedure. This is deemed of importance, also in light of the fact that the final results from Study 110 Treatment Period 1 will be used to provide additional context to the disease progression patterns observed in the analyses of US CFFPR and ECFSPR data within the PAES study in the 2-5 years age range.

The MAH clarified that, apart from the results of Treatment Period 2, the only differences between the Study 110 Treatment Period 1 CSR (dated 25 February 2019; previously submitted within variation EMEA/H/C/003954/II/0049) and Study 110 Final CSR (dated 24 August 2020) are minimal consisting of clarifications or correction of typos. No changes or updates to the Treatment Period 1 data or results discussion were made in the Study 110 Final CSR.

Treatment Period 2 was optional for subjects enrolled at 3 sites in France. All the 10 subjects who were <12 years of age at the end of the 96 weeks of Treatment Period 1, opted to enrol in Treatment Period 2 of the study to receive up to 168 weeks (approximately) of additional LUM/IVA treatment, for continued assessment of safety.

All 10 subjects enrolled in Treatment Period 2 discontinued prematurely from Treatment Period 2 (prior to the foreseen 168 weeks of additional LUM/IVA treatment), when commercial drug became available for children 6 through 11 years of age in France. The maximum treatment duration in Treatment

Period 2 was up to approximately 89 weeks (624 days) of additional LUM/IVA treatment; the mean and median treatment duration was 414.8 days and 426.5 days (ranging from 80 to 624 days), respectively.

Although this is a very small subgroup and therefore making a comparison has key limits, the baseline characteristics at parent study baseline of this small subgroup entering Treatment period 2 were similar to the overall population with the exception of being younger (7.6 years range: 6 to 9 years as compared to 8.9 range 6-12) and as a consequence of having the anthropometric measures slightly lower than those of the overall population. The baseline disease characteristics were similar i.e. sweat chloride or even indicating milder lung disease i.e. ppFEV1.

Efficacy outcomes were not assessed in treatment Period 2.

As regards to safety in Treatment Cohort Period 2, most subjects (90.0%) had at least 1 AE however these were mild or moderate in severity; no deaths or SAE occurred. No subject had AEs that were considered related or possibly related to study drug, AE leading to treatment discontinuation, or AE leading to treatment interruption.

No clinically meaningful adverse changes or trends were observed for laboratory or vital sign measurements and specifically there were no transaminase elevations >3 × ULN.

In these 10 subjects that received up to approximately 89 weeks of additional LUM/IVA treatment, no new safety concerns were identified. In Tables reporting AEs by PT, a subject with multiple events within a category was counted only once in that category, thus numbers may be misleading; for example the PT of infective PEX of CF are 4 (40%) but PEx occurred more than one time in 2 out of 4 subjects; in a third subject one event of PEx and a further event of Pneumopathy/ Radiological Focus on the left base of the lung occurred. Due to the limited number (N=10) of subjects enrolled in Treatment Cohort Period 2, the variable treatment duration in each subject (treatment duration ranged from 80 to 624 days) and due to multiple events counted only once within each category, no conclusion may be drawn on the frequencies of AEs observed in this study.

2. CHMP overall conclusion and recommendation

☒ **Fulfilled: No regulatory action required.**

3. Additional clarification requested

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

1. The MAH should clarify if, apart from the results of Treatment Period 2, there are other differences between Study 110 Treatment Period 1 CSR (dated 25 February 2019), previously submitted within variation EMEA/H/C/003954/II/0049, and Study 110 Final CSR (dated 24 August 2020), submitted by the MAH within this procedure. Differences between the two CSR should be highlighted and adequately discussed.
2. The MAH should provide mean and median treatment duration in Treatment Period 2, for the 10 patients enrolled in Treatment Period 2
3. The MAH should clarify what kind of abnormal findings were reported in the subject with previous normal Ophthalmological Examinations, that had abnormal lens findings on both eyes at the Early Termination of Treatment visit and provide information on the follow up of this event i.e. resolved/not.

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

4. MAH responses to Request for supplementary information

Question 1

1. The MAH should clarify if, apart from the results of Treatment Period 2, there are other differences between Study 110 Treatment Period 1 CSR (dated 25 February 2019), previously submitted within variation EMEA/H/C/003954/II/0049, and Study 110 Final CSR (dated 24 August 2020), submitted by the MAH within this procedure. Differences between the two CSR should be highlighted and adequately discussed.

Summary of the Applicant's Response

Apart from the results of Treatment Period 2, the only differences between the Study 110 Treatment Period 1 CSR (dated 25 February 2019; previously submitted within variation EMEA/H/C/003954/II/0049) and Study 110 Final CSR (dated 24 August 2020) are:

• the study description was edited to clarify the completion of Treatment Period 2;

• references to "Treatment Cohort" were updated to "Treatment Cohort Period 1" throughout to clearly differentiate from the Treatment Cohort Period 2 data;

• Section 9.8.1.1 was added to summarize the changes in study conduct due to the COVID-19 pandemic; and

• typographical errors were corrected.

No changes or updates to the Treatment Period 1 data or results discussion were made in the Study 110 Final CSR.

Assessment of the MAH's Response

The MAH provided the requested clarifications.

Issue resolved

Question 2

2. The MAH should provide mean and median treatment duration in Treatment Period 2, for the 10 patients enrolled in Treatment Period 2

Summary of the Applicant's Response

For the 10 subjects enrolled in Treatment Period 2, the mean treatment duration was 414.8 days and the median treatment duration was 426.5 days.

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Protocol VX15-809-110: Treatment Cohort Period 2

Ad Hoc Table ah.14.1.8a2
Summary of Exposure - Treatment Cohort Period 2
All Enrolled Subjects for Treatment Cohort Period 2

	Overall N = 10
Total exposure (patient years)	12.3
Exposure duration (days)	
n	10
Mean (SD)	414.8 (184.51)
SE	58.35
Median	426.5
Min, Max	80, 624

- N: Number of subjects enrolled in the Study 110 Treatment Cohort Period 2.
- Duration of study drug exposure (days) = Last dose date during Treatment Cohort Period 2 - first dose date during Treatment Cohort Period 2 + 1.

Assessment of the MAH's Response

The MAH provided the requested data.

Issue resolved

Question 3

3. The MAH should clarify what kind of abnormal findings were reported in the subject with previous normal Ophthalmological Examinations, that had abnormal lens findings on both eyes at the Early Termination of Treatment visit and provide information on the follow up of this event i.e. resolved/not.

Summary of the Applicant's Response

Vertex has followed up with the site and ophthalmologist regarding the subject who had an abnormal lens finding on both eyes (though no lens opacity was reported; Study 110 CSR/ Listing 16.2.8.3a2) for the ophthalmological examination (OE) at the Early Termination of Treatment (ETT) visit. The ophthalmologist has confirmed that the original worksheet was filled out incorrectly and that the lenses for both eyes were normal at the ETT visit.

A Study 110 CSR errata page correcting the error regarding the abnormal lens findings at the ETT visit for in the Study 110 Final CSR is submitted with this response.

Assessment of the MAH's Response

The MAH followed up with the site and ophthalmologist regarding the subject who had an abnormal lens finding on both eyes at the Early Termination of Treatment visit.

The ophthalmologist has confirmed that the original worksheet was incorrectly reported as abnormal and that the lenses for both eyes of that subject were normal at the ETT visit.

Issue resolved