![European Medicines Agency — Science Medicines Health]

14 September 2017
EMA/717352/2018
Human Medicines Evaluation Division

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/P46/009.1

Note

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

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Orkambi 100mg/125mg film-coated tablet

International non-proprietary name: Lumacaftor/ivacaftor

Procedure no.: EMEA/H/C/003954

Marketing authorisation holder (MAH): Vertex Pharmaceuticals (Europe) Ltd.

Rapporteur:	Greg Markey (UK)
Start of the procedure:	28 November 2016
Date of this report:	20 August 2017
Deadline for Rapporteur's AR:	21 August 2017
Deadline for CHMP member's comments:	04 September 2017
Date of the Rapporteur's updated report:	07 September 2017

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Administrative information

Invented name of the medicinal product:	**Orkambi 100mg/125mg film-coated tablet**
INN (or common name) of the active substance(s):	Lumacaftor/ivacaftor
MAH:	Vertex Pharmaceuticals (UK) Ltd
Currently approved Indication(s)	Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F*508del* mutation in the CFTR gene
Pharmaco-therapeutic group (ATC Code):	R07AX30
Pharmaceutical form(s) and strength(s):	Film-coated tablet: Lumacaftor 100mg, ivacaftor 125mg FDC tablet
Rapporteur's contact person: Names of Rapporteur Assessors:	**Name:** Mr. Graham Searle Tel: +44 (0)203-080-7709 Email: graham.searle@mhra.gsi.gov.uk **Clinical:** **Name:** Dr. Ming-Yuan Tseng Tel: +44 (0)203-080-7342 Email: Ming-Yuan.Tseng@mhra.gsi.gov.uk **Pharmacokinetics** **Name:** Dr. Justin Pittaway-Hay Tel: +44 (0)203-080-6141 Email: Justin.Pittaway-Hay@mhra.gsi.gov.uk **Statistics** **Name:** Dr. Khadija Rantell Tel: +44 (0)203-080-6971 Email: Khadija.Rantell@mhra.gsi.gov.uk

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1. Introduction

Study VX13-809-011 (Study 011) was submitted under Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation'). There were two parts in the study: Part A & Part B.

Part A: A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics (PK) and Safety of Lumacaftor in Combination with Ivacaftor in Subjects 6 through 11 Years of Age with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, was initiated on 12 July 2013 and completed on 25 October 2013. Ten patients received at least 1 dose of LUM/IVA (LUM 200 mg/IVA 250 mg q12h) for 14 days.

Part B: A Phase 3, Open-Label Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Lumacaftor in Combination with Ivacaftor in Subjects 6 through 11 Years of Age with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, was added in September 2013, initiated on 15 January 2015, and completed on 28 October 2015. Fifty-eight patients received at least 1 dose of LUM/IVA (LUM 200 mg/IVA 250 mg q12h) for 24 weeks.

Study 011 Part A was included in the original LUM/IVA paediatric investigation plan (PIP) and results were reviewed by the Paediatric Committee (PDCO) in the PIP compliance check (C1-001582-PIP01-13), which was confirmed on 14 November 2014 (EMA/604209/2014).

Study 011 Part B was not included in the original LUM/IVA PIP. Results from both Parts A and B were submitted to the PDCO on 4 April 2016 with LUM/IVA PIP Modification 4 (EMEA-001582-PIP01-13-M04) for supporting the initiation of Study VX15-809-115 (PIP Study 15), a safety and pharmacokinetics (PK) study evaluating LUM/IVA in subjects 2 through 5 years of age, with cystic fibrosis (CF), homozygous for F508del, which was initiated in the USA already. The PDCO was not able to agree with the dose proposed, because Study VX14-809-109 was still ongoing, and the validity of pop PK model and the body weight distribution for children with CF aged 2-6 years were not fully clarified. The discussion in the PDCO will continue in 2017.

2. Scientific discussion

Information on the development program

Orkambi™ (LUM 200 mg/IVA 125 mg FDC tablet) was approved in the European Union (EU) through a centralized procedure on 19 November 2015 for the treatment of CF in patients aged 12 years and older with a homozygous F508del mutation in the CFTR gene.

The Applicant continued the development program in patients aged 6-11 years. In addition to Study 011, two other studies targeted the same population:

- Study VX14-809-109 (Study 109; study completed, data analysis ongoing): a Phase 3, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LUM/IVA combination therapy in subjects 6 through 11 years of age with CF, homozygous for F508del. Study 109 enrolled more than 200 subjects; subjects were administered LUM 200 mg/IVA 250 mg q12h for 24 weeks.

- Study VX15-809-110 (Study 110; ongoing): a Phase 3 rollover study to evaluate the safety and efficacy of long-term treatment with LUM/IVA combination therapy in subjects aged 6 years and older with CF, homozygous for F508del. Study 110 has enrolled subjects from Studies 011 Part B and 109. Subjects are administered LUM 200 mg/IVA 250 mg q12h (subjects 6 through 11 years of age) or LUM 400 mg/IVA 250 mg q12h (subjects 12 years of age and older) for 96 weeks.

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The Applicant intends to submit a Line Extension to the European Medicines Agency (EMA) in Q2 2017 to extend the current indication to include CF patients aged 6 through 11 years, homozygous for F508del, with new tablet strength (LUM 100 mg/IVA 125 mg FDC tablets). The extension of this indication will be supported by final results from Studies 011 and 109, and interim analysis results from Study 110.

Information on the pharmaceutical formulation used in the study

Subjects in Studies 011 received LUM 200 mg/IVA 250 mg q12h.

- Part A: lumacaftor (LUM) 200-mg/ivacaftor (IVA) 125-mg fixed-dose combination (FDC) tablet + IVA 125-mg tablet

- Part B: LUM 100 mg/IVA 125-mg FDC tablet

For completeness, a summary of the LUM/IVA and IVA formulations used in Studies 011, 109, and 110 is provided in Table 1:

Table 1   Formulations in Studies 011, 109, and 110

Time	Formulation
Study 011 Part A	
AM	1 film-coated FDC tablet of LUM 200 mg/IVA 125 mg AND 1 film-coated tablet of IVA 125 mg
PM	1 film-coated FDC tablet of LUM 200 mg/IVA 125 mg AND 1 film-coated tablet of IVA 125 mg
Studies 011 Part B and 109	
AM	2 film-coated FDC tablets of LUM 100 mg/IVA 125 mg
PM	2 film-coated FDC tablets of LUM 100 mg/IVA 125 mg
Study 110	
Subjects 6 through 11 years of age	
AM	2 film-coated FDC tablets of LUM 100 mg/IVA 125 mg
PM	2 film-coated FDC tablets of LUM 100 mg/IVA 125 mg
Subjects 12 years of age and older	
AM	2 film-coated FDC tablets of LUM 200 mg/IVA 125 mg
PM	2 film-coated FDC tablets of LUM 200 mg/IVA 125 mg

FDC: fixed-dose combination; IVA: ivacaftor; LUM: lumacaftor

Pharmacokinetics

There is no clinically relevant difference in PK parameters for lumacaftor or ivacaftor between males and female subjects.

- Absorption

   After twice-daily dosing, steady-state plasma concentrations of lumacaftor and ivacaftor were generally reached after approximately 7 days of treatment. The steady-state exposure of ivacaftor is lower than that of Day 1 due to the CYP3A induction effect of lumacaftor.

   Following multiple oral doses of lumacaftor, the exposure of lumacaftor generally increased proportional to dose over the range of 50 mg to 1000 mg every 24 hours. The exposure of lumacaftor increased approximately 2.0-fold when given with fat-containing food relative to fasted conditions.

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Following multiple oral dose administration of ivacaftor in combination with lumacaftor, the exposure of ivacaftor generally increased with dose from 150 mg every 12 hours to 250 mg every 12 hours. The exposure of ivacaftor when given in combination with lumacaftor increased approximately 3-fold when given with fat-containing food.

- Distribution

Lumacaftor is approximately 99% bound to plasma proteins, primarily to albumin.

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin.

- Biotransformation

Lumacaftor is not extensively metabolised in humans, with the majority of lumacaftor excreted unchanged in the faeces.

Ivacaftor is extensively metabolised in humans, primarily by hepatic CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active.

- Elimination

Following oral administration of lumacaftor, the majority of lumacaftor (51%) is excreted unchanged in the faeces. There was negligible urinary excretion of lumacaftor as unchanged drug. The apparent terminal half-life is approximately 26 hours.

Following oral administration of ivacaftor, the majority of ivacaftor (87.8%) is eliminated in the faeces after metabolic conversion. There was negligible urinary excretion of ivacaftor as unchanged drug. In healthy subjects, the half-life of ivacaftor when given with lumacaftor is approximately 9 hours.

- Hepatic impairment

Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had higher exposures (AUC0-12hr by approximately 50% and Cmax by approximately 30%) compared with healthy subjects matched for demographics.

Pharmacodynamics

- Effects on Sweat Chloride:

Changes in sweat chloride in response to lumacaftor alone or in combination with ivacaftor were evaluated in a double-blind, placebo-controlled, Phase 2 clinical trial in patients with CF age 18 years and older. In this trial, 10 patients (homozygous for F508del-CFTR mutation) completed dosing with lumacaftor alone 400 mg q12h for 28 days followed by the addition of ivacaftor 250 mg q12h for an additional 28 days, and 25 patients (homozygous or heterozygous for F508del) completed dosing with placebo. The treatment difference between lumacaftor 400 mg q12h alone and placebo evaluated as mean change in sweat chloride from baseline to Day 28 was statistically significant at -8.2 mmol/L (95% CI: -14, -2). The treatment difference between the combination of lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo evaluated as mean change in sweat chloride from baseline to Day 56 was statistically significant at -11 mmol/L (95% CI: -18, -4).

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- Changes in FEV1:

  The treatment difference between lumacaftor 400 mg q12h alone and placebo evaluated as mean absolute change in ppFEV1 was <u>-4.6 percentage points (95% CI: -9.6, 0.4) from baseline to Day 28</u>, 4.2 percentage points (95% CI: −1.3, 9.7) from baseline to Day 56, and 7.7 percentage points (95% CI: 2.6, 12.8; statistically significant) from Day 28 to Day 56.

- Decrease in Heart Rate

  During the 24-week, placebo-controlled, Phase 3 studies, a maximum decrease in mean heart rate of 6 beats per minute (bpm) from baseline was observed on Day 1 and Day 15 around 4 to 6 hours after dosing. From Week 4, the change in mean heart rate at pre-dose ranged from 1 to 2 bpm below baseline among patients treated with lumacaftor/ivacaftor. The percentage of patients with heart rate values <50 bpm on treatment was 11% for patients who received lumacaftor/ivacaftor, compared to 4.9% for patients who received placebo.

<u>Safety</u>

Orkambi is generally well tolerated; the most frequently reported adverse events by patients aged 12 years and older in the pooled, placebo-controlled Phase 3 studies, were dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo).

Serious adverse reactions occurring in at least 0.5% of patients included hepatobiliary events, e.g., transaminase elevations, cholestatic hepatitis and hepatic encephalopathy.

- Hepatic Events

  During the 24-week, placebo-controlled, Phase 3 studies, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN were <u>0.8%, 2.0%, and 5.2%</u> in lumacaftor/ivacaftor treated patients vs. 0.5%, 1.9%, and 5.1% in placebo-treated patients. The incidence of transaminase-related adverse reactions was 5.1% vs. 4.6% in lumacaftor/ivacaftor vs. placebo. Following discontinuation of lumacaftor/ivacaftor, liver function tests returned to baseline or improved substantially in all patients.

- Respiratory Events

  During the 24-week, placebo-controlled, Phase 3 studies, the incidence of respiratory adverse reactions (e.g., chest discomfort, dyspnoea, and respiration abnormal) was 26.3% vs, 17.0% in lumacaftor/ivacaftor vs. placebo. Approximately three-quarters of the events began during the first week of treatment, and in most patients the events resolved without dosing interruption.

- Cardiovascular Events

  During the 24-week, placebo-controlled, Phase 3 studies, adverse reactions related to increased blood pressure (BP) (e.g., hypertension, BP increased) were reported in 0.9% (7/738) of patients treated with lumacaftor/ivacaftor vs. none who received placebo.

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Clinical aspects

The MAH submitted a final study report for:

Study VX13-809-011 (Study 011): A Phase 3, Open-Label Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Efficacy of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Objectives

Part A

Primary:

-   To evaluate the PK of multiple doses of lumacaftor in combination with ivacaftor

Secondary:

-   To investigate the PK of a lumacaftor metabolite, M28 (M28-lumacaftor), and ivacaftor metabolites, M1 and M6 (M1-ivacaftor and M6-ivacaftor)
-   To evaluate the safety and tolerability of multiple doses of lumacaftor in combination with ivacaftor

Part B

Primary:

-   To evaluate the safety and tolerability of lumacaftor in combination with ivacaftor through Week 24.

Secondary:

-   To evaluate the PD of lumacaftor in combination with ivacaftor through Week 24
-   To evaluate the off-drug response after the Washout Period (Week 24 to Week 26)
-   To evaluate the PK of lumacaftor, M28-lumacaftor, ivacaftor, M1-ivacaftor, and M6-ivacaftor for lumacaftor in combination with ivacaftor
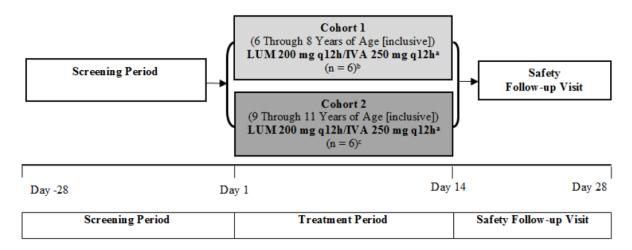
Study design

This was a 2-part (Part A and Part B), open-label, multicenter study that evaluated the PK, safety, tolerability, and PD of multiple doses of LUM/IVA in subjects 6 through 11 years of age (inclusive) with CF who are homozygous for the F508del-CF transmembrane conductance regulator (CFTR) mutation.

Part A

Screening Visit assessments were completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of the study drug (Day 1). During the Treatment Period, subjects were administered LUM 200 mg every 12 hours (q12h)/IVA 250 mg q12h for 14 days. A Safety Follow-up Visit was scheduled to occur 10 ($\pm$ 4) days after the last dose of study drug.

Part A evaluated PK, safety, and tolerability for 14 days. Primary endpoints of Part A were LUM and IVA PK parameters, including maximum observed concentration (Cmax) and area under the concentration versus time curve from time of dosing to time tau ($AUC_{0-\tau}$). Based on confirmation of safety and adequate exposure (i.e., comparable exposure with subjects 12 years of age and older) with LUM 200 mg/IVA 250 mg q12h in Part A, this dose regimen was selected for Part B.

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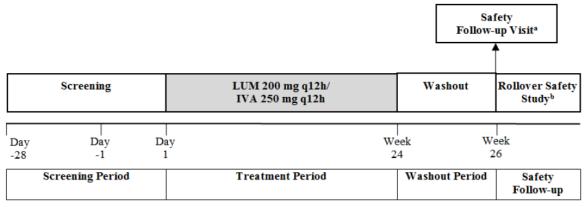IVA: ivacaftor; LUM: lumacaftor; n: number of subjects; q12h: every 12 hours.
Note: A minimum of 9 subjects must have completed the study.
a   Study drug was administered from Day 1 through Day 14. On Day 14, only the morning dose of study drug was administered.
b   A minimum of 3 subjects 6 through 8 years of age (inclusive) must have completed the study.
c   A minimum of 3 subjects 9 through 11 years of age (inclusive) must have completed the study.

Part B

Screening Visit assessments were completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of study drug (Day 1). During the Treatment Period, subjects were administered LUM 200 mg q12h/IVA 250 mg q12h for 24 weeks. A 2-week Washout Period (Week 24 ± 5 days to Week 26 ± 3 days) was included in order to evaluate the off-drug response.

Primary endpoints for Part B were safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations, and spirometry.

IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours.
a   The Week 26 Safety Follow-up Visit was scheduled to occur 2 weeks (± 3 days) after the last dose of study drug. The Week 26 Safety Follow-up Visit was not required for subjects who permanently discontinued study drug treatment before the Week 16 Visit.
b   At the Week 26 Safety Follow-up Visit, subjects who completed the visits in the Treatment Period, regardless of whether they had permanently discontinued study drug treatment, were offered the opportunity to enroll in an optional open-label Rollover Safety Study evaluating LUM/IVA. Subjects who discontinued treatment were only eligible for the Observational Cohort and not the Treatment Cohort in the Rollover Safety Study.

An independent data monitoring committee (DMC) was formed using the Cystic Fibrosis Foundation Data Safety Monitoring Board. The DMC objectives and operational details were defined in a separate document (DMC Charter), which was finalized before the first subject is enrolled in Part B of the study.

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The DMC conducted one review of the study safety data, with the same data snapshot date as the one used for the interim analysis. Details of the DMC analysis followed IA Analysis as provided in the IA Analysis Plan Version 2 (dated Aug. 26, 2015).

An interactive web response system (IWRS) was used to assign subject identification numbers and manage drug supply at the site. From the time of subject identification number assignment, and throughout the duration of the study, subjects were identified by their initials and assigned subject identification number.

Subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not have been informed of their study-related spirometry and LCI (Part B only) results during the Treatment Period, regardless of whether the subject permanently discontinued treatment.

Statistical Assessor's Comment:

The involvement of DCM to monitor safety is endorsed. The Applicant is requested to provide the minutes from the DCM meeting.

The strategies used by the Applicant to minimise bias are acknowledged.

Study population

Table 2   Principal Inclusion Criteria and Enrollment of Subjects With CF in Study 011

Enrollment Criteria	Study 011
Confirmed diagnosis of CF[1]	2 CF-causing mutations (all as documented in the subject's medical record) and either chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities (Parts A and B)
CFTR mutation on both alleles	*F508del* (Parts A and B)
Age	6 through 11 years of age (Parts A and B)
ppFEV$_1$ at screening[a]	70 through 105 (Part A) and ≥40 (Part B)

Source: VX13-809-011 CSR/Sections 9.1 and 9.3.1
CF: cystic fibrosis; ppFEV$_1$: percent predicted forced expiratory volume in 1 second
[a]   Given the favorable safety profile in Study 011 Part A (VX13-809-011 CSR/Section 13.3.1), the modification of inclusion criteria (from a ppFEV$_1$ of 70 through 105 in Part A to ≥40 in Part B) was confirmed before the start of Part B. Percent predicted FEV$_1$ values were determined using the Wang equation.[2]

Subjects who are homozygous for the F508del-CFTR mutation (genotype was confirmed at the Screening Visit) in Part A may wish to participate in Part B.

Key exclusion criteria:

- Subjects with a history of any illness or condition that could confound study results or pose an additional safety risk.

- Subjects with protocol-defined laboratory values indicative of abnormal liver function or abnormal renal function.

Abnormal liver function was defined as any 3 or more of the following:

Part A only

≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST)

≥3 × ULN alanine aminotransferase (ALT)

≥3 × ULN gamma-glutamyl transpeptidase

≥3 × ULN alkaline phosphatase

≥2 × ULN total bilirubin

Part B only

        ALT or AST >5 × ULN, or bilirubin >2 × ULN

Sample Size and Power

Part A

- No formal sample size calculations; the size is deemed adequate to meet the PK objectives.

Part B

- With a total sample size of 50 subjects completed, <u>there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%</u>. The probabilities are binomial, determined based on expected availability of subjects at the sites with the capability of assessing LCI.

Table 9-11   **Probability of Observing Adverse Events in at Least 1 Subject if the Adverse Event Incidence Rate (θ) is 5% and 10%**

Sample Size	θ = 5%	θ = 10%
50[a]	92.3%	99.5%

[a]   50 reflects the sample size of the completers.

> **Statistical Assessor's Comment:**
>
> *The strategy used to determine sample size is in line with the primary objective of Part B of the study.*

Treatments

Part A

LUM 200 mg q12h/IVA 250 mg q12h (1 × LUM 200-mg/IVA 125-mg fixed-dose tablet [lot B13030] q12h + 1 × IVA 125-mg tablet [lot 3106243R] q12h) was administered orally.

Part B

LUM 200 mg q12h/IVA 250 mg q12h (2 × LUM 100-mg/IVA 125-mg fixed-dose tablet [lot 6041337] q12h) was administered orally.

Endpoints

Part A

Primary Endpoint

- Lumacaftor and ivacaftor PK parameters, including maximum observed concentration (Cmax) and area under the concentration versus time curve from time of dosing to time tau (AUC0-т)

Secondary Endpoints

- M28-lumacaftor, M1-ivacaftor, and M6-ivacaftor PK parameters, including Cmax and AUC0-т

- Safety and tolerability of lumacaftor in combination with ivacaftor as determined by AEs, clinical laboratory values.

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Part B

<u>Primary Endpoint</u>

- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmological examinations, and spirometry

<u>Secondary Endpoints</u>

- Average absolute change from baseline in sweat chloride at Day 15 and at Week 4

- Absolute change from baseline in <u>body mass index (BMI)</u> and BMI-for-age z-score at Week 24

- PK parameters of lumacaftor, M28-lumacaftor, ivacaftor, M1-ivacaftor, and M6-ivacaftor

- Absolute change from baseline in weight and weight-for-age z-score at Week 24

- Absolute change from baseline in height and height-for-age z-score at Week 24

- Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at Week 24

- Absolute change from baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) domains at Week 24

- Absolute change in sweat chloride from Week 24 at Week 26

Sweat samples were sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results were not to be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory were provided separately. The sweat chloride test must have been conducted pre-dose relative to the morning dose of study drug during the Treatment Period. At each time point, 2 samples were collected, 1 sample from each arm (left and right). Of the 2 measurements, only the sweat chloride value obtained from a sample volume ≥15 μL was included in any analysis. If a subject has replicated measurements at a post-baseline time point, then the median of the values was used in data analyses. The sweat chloride results for the left and right arms were averaged and used in the analysis, if the sweat chloride values for the left and right arms were both ≥15 μL; if only 1 arm is ≥15 μL, then only that value will be used. The baseline was defined as the average of the measurements at screening and on Day 1 pre-dose.

The z-score for BMI, weight, and height were calculated using Centre for Disease Control and Prevention (CDC) growth charts.

To calculate the score for each domain, the response scores on the negatively phrased questions were reversed (reversed scores = 5 − response scores). Therefore, 1 always represents the worst condition and 4 always represents the best condition. In each domain, in cases where individual questions were skipped, the missing scores were imputed with the mean score of the non-missing questions for that domain rounded to the nearest integer. The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition).

Statistical Assessor's Comment:

The use of central laboratory for assessment of sweat is endorsed, especially given the open label nature of the study design. When replicate measurements are available, the Applicant is requested to use the worst values rather the median values in the analysis.

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Sampling

<u>PK Assessments</u>

Part A

For the evaluation of plasma concentrations of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA, blood samples were collected from all subjects as follows:

• Day 1: before the morning dose and at 2, 4, 6, and 12 hours after the morning dose

• Day 7: before the morning dose

• Day 14: before the morning dose and at 4, 6, and 12 hours after the morning dose

• Day 15: any time between 24 to 96 hours after the morning dose on Day 14

Part B

For the evaluation of plasma concentrations of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA, blood samples were collected from all subjects as follows:

• Day 1 and Week 4: before the morning dose and 3 to 6 hours after the morning dose

• Day 15: any time 3 to 6 hours after the morning dose

• Week 16: before the morning dose

• Week 24: collected at the same time as other blood collections

Statistical Methods

Pharmacokinetics:

Part A and Part B

Phoenix® WinNonlin® Professional Edition Version 5.3 or higher, located on the validated Citrix Production Server, was used for evaluating drug concentrations and generating PK parameters. PK analyses were performed on the entire population given a dose of LUM, whether the subject completed dosing or not and if the dataset(s) supported those analyses. PK parameters were determined using standard non-compartmental analysis (NCA).

Table 9-17   Pharmacokinetic Parameter Output Selection

Parameter	Units	Definition
Part A		
C_{max}	concentration (e.g., ng/mL)	maximum observed concentration
t_{max}	time (e.g., h)	time of the maximum concentration
C_{trough}	concentration (e.g., ng/mL)	predose concentration
Part B		
C_{3-6h}	concentration (e.g., ng/mL)	observed concentration at 3 to 6 hours postdose
C_{trough}	concentration (e.g., ng/mL)	predose concentration

Note: See Section 9.8.2.2 for changes regarding the calculation of PK parameters.

Pharmacodynamics (Part B only):

PD analyses were performed using the FAS for the following secondary PD endpoints:

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(1) average absolute change from baseline in sweat chloride at Day 15 and at Week 4;

(2) absolute change from baseline in BMI and BMI-for-age z-score at Week 24;

(3) absolute change from baseline in weight and weight-for-age z-score at Week 24;

(4) absolute change from baseline in height and height-for-age z-score at Week 24;

(5) absolute change from baseline in CFQ-R respiratory domain score at Week 24;

(6) absolute change from baseline in TSQM domains at Week 24; and

(7) absolute change in sweat chloride from Week 24 at Week 26.

The analysis for the average absolute change from baseline in sweat chloride at Day 15 and at Week 4 is based on a mixed model repeated measures (MMRM), including absolute change from baseline in sweat chloride as the dependent variable (including all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation), visit as fixed effects, with adjustment for sex (male versus female), baseline weight group (< median versus ≥ median), and percent predicted forced expiratory volume in 1 second (ppFEV1) severity at screening (<90, and ≥90); baseline sweat chloride as a covariate; and subject as a random effect. The primary result obtained from the model was the average treatment effect at Day 15 and at Week 4.

Analyses for other PD endpoints are based on similar MMRMs, with the baseline sweat chloride replaced by baseline of the corresponding variable. For the analysis of BMI, weight, and their z-scores, the MMRM models remove the baseline weight group from the covariates.

The absolute change in sweat chloride from Week 24 at Week 26 was analyzed using a linear regression. The regression model included the absolute change in sweat chloride from Week 24 at Week 26 as the dependent variable; with adjustment for sex (male versus female), baseline weight group (< median versus ≥ median), and ppFEV1 severity at screening (<90, and ≥90); and sweat chloride at Week 24 as a covariate.

Statistical Assessor's Comment:

The use of MMRM model is appropriate for analysing longitudinal data as it accounts for the correlations within subjects and allow unequal number of observations per subject. However, the issues of how missing data were handled in these analyses should be explored, as the MMRM model assumes data that are missing are missing at random. This assumption cannot be checked but it is possible to conduct alternative analyses that do not make this assumption, for example by imputing missing data using the baseline observation carried forward (BOCF) and see if the conclusions drawn from these analyses are similar to this analysis. Given the very low number of missing data in this study, additional analyses are unlikely to change the study conclusion.

The inclusion of prognostic variable in the model enhances precision and is therefore supported.

The Applicant is requested to explain why the change from baseline to Day 15 and Week 4 was calculated using the average of Day 15 and Week 4.

Exploratory LCI Analyses (Part B only)

The analyses of LCI (LCI2.5 and LCI5.0) are based on MMRMs similar to the primary analysis for sweat chloride, replacing baseline sweat chloride with baseline LCI.

Subgroup analysis

Subgroup analyses were performed for the following groups:

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- Age (<9 years, and ≥9 years)

- ppFEV1 severity at screening (<90, and ≥90)

- ppFEV1 severity at baseline (<90, and ≥90)

- Sex (female and male)

- Weight at baseline (< median, and ≥ median)

- Prior use of inhaled antibiotic (Yes, and No)

- Prior use of inhaled bronchodilator (Yes, and No)

- Prior use of inhaled bronchodilator (Short-Acting Only, versus [Short-Acting and

- Long-Acting] or Long-Acting only, versus No)

- Prior use of inhaled hypertonic saline (Yes, and No)

- Prior use of inhaled corticosteroids (Yes, and No)

- Pseudomonas aeruginosa status at baseline (Positive, and Negative)

- Prior use of dornase alpha (Yes, and No)

Statistical Assessor's Comment:

The subgroup analyses are supported.

Safety:

For both Part A & Part B

Safety analyses were performed for the Safety Set. Only a descriptive analysis of safety was performed.

Rapporteur's Comments

This is a PK/dose and safety study to be followed by - Study VX14-809-109 (Study 109; study completed, data analysis ongoing): a Phase 3, double-blind, placebo-controlled, parallel-group study. Neither Part A nor Part B was an efficacy-confirmatory study.

The eligibility criteria seemed to allow patients who completed Part A to continue Part B, though the long-term safety profile in the target population was not yet defined. Further, it is not clear why the exclusion criterion based on hepatic transaminase was less stringent in Part B than in Part A. It is not clear why Part B was not included in the PIP, given the PIP compliance check was conducted in 2014.

Results

Recruitment/ Number analysed

Part A

A total of 10 subjects, including 5 aged 6 through 8 years and 5 aged 9 through 11 years, were enrolled, completed dosing and the study. These 10 subjects were included in all Data Sets.

Part B

A total of 58 subjects were enrolled from 20 sites in North America, with 54 (93.1%) subjects completing treatment and completing the study.

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The Full Analysis Set (FAS) and the Safety Set included all 58 enrolled subjects exposed to any quantity of study drug. The PK Set included 57 enrolled subjects for whom the primary PK data were considered to be sufficient and interpretable.

A total of 30 subjects were enrolled in the LCI Sub-study, exposed to study drug, with 28 (93.3%) subjects completing treatment and 27 (90.0%) subjects completing the study.

Table 10-2   Summary of Subject Disposition (Part B, All Subjects Set)

	n (%)[a]		
Disposition/Reason	< Median Weight N = 28	≥ Median Weight N = 30	Overall N = 58
All Subjects Set[b]	28	30	58
Full Analysis Set[c]	28	30	58
Safety Set[d]	28	30	58
Enrolled but never dosed	0	0	0
Completed treatment[e]	25 (89.3)	29 (96.7)	54 (93.1)
Discontinued treatment	3 (10.7)	1 (3.3)	4 (6.9)
AE	2 (7.1)	0	2 (3.4)
Subject refused further dosing (not due to an AE)	0	1 (3.3)	1 (1.7)
Did not meet eligibility criteria[f]	1 (3.6)	0	1 (1.7)
Last completed on-treatment scheduled visit			
Day 1	0	1 (3.3)	1 (1.7)
Day 15	2 (7.1)	0	2 (3.4)
Week 20	1 (3.6)	0	1 (1.7)
Completed study[e]	26 (92.9)	28 (93.3)	54 (93.1)
Discontinued study	2 (7.1)	2 (6.7)	4 (6.9)
AE	1 (3.6)	0	1 (1.7)
Withdrawal of consent (not due to an AE)	0	2 (6.7)	2 (3.4)
Physician decision	1 (3.6)	0	1 (1.7)

Source: Table 14.1.1.1b.
AE: adverse event; n: number of subjects; N: number of subjects in the Safety Set.
Note: The median weight was 30.6 kg.
[a]   The percentages are calculated relative to the number of subjects in the Safety Set.
[b]   All Subjects Set: All subjects who enrolled or dosed.
[c]   Full Analysis Set: All enrolled subjects who received any amount of study drug.
[d]   Safety Set: All subjects who received any amount of study drug.
[e]   Refer to Listing 16.2.1b for individual subjects who did not complete treatment and/or the study.
[f]   There was 1 important protocol deviation related to inclusion criteria (subject was not homozygous for F508del [Section 10.5.2]). All other subjects were eligible for inclusion in Part B (Listing 16.2.4.3b and Listing 16.2.8.1.5.2b).

Statistical Assessor's Comment:

Only 7% (4/58) who received treatment withdrew prior to Week 24.

There were 7 subjects with important protocol deviations during Part B of the study. The impact of these deviations on the assessment of secondary endpoints should be investigated.

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Baseline data

Part A

- The median weight across all 10 subjects was 26.50 kg at baseline.

- The mean FEV1 and ppFEV1 values across all 10 subjects were 1.521 L and 89.42 at baseline.

Part B

- Subjects enrolled were male (27 [46.6%] subjects) and female (31 [53.4%] subjects). All subjects were White.

- The median age was 9 years (range: 6 to 12 years) with 22 (37.9%) subjects <9 years of age and 36 (62.1%) subjects ≥9 years of age.

- The median weight was 30.6 kg (range: 18.2 to 57.0 kg) with 28 subjects < median weight and 30 subjects ≥ median weight.

- The mean values were 105.9 mmol/L (sweat chloride), 91.4 (ppFEV1), 16.89 kg/m2 (BMI), 0.01 (BMI z-score), -0.03 (weight z-score), and 0.03 (height z-score).

- A total of 25 (43.1%) subjects were positive for Pseudomonas aeruginosa at baseline.

PHARMACOKINETIC EVALUATION

Part A

- The PK Set contained data for 10 subjects.

- Day 1 pre-dose samples from one Subject and another Subject and Day 7 pre-dose samples from a different Subject were excluded from the calculation due to the PK samples being taken after the dose was administered. The samples were included for the NCA using the actual sampling time.

- The Day 14, 4-hour time point value from one Subject and the Day 14, 12-hour time point value for another Subject were missing because the subjects did not have a PK sample drawn at the specified time points on Day 14.

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Figure 11-1   Mean Lumacaftor Concentration Versus Time Profiles on Day 1 and Day 14 After Administration of Lumacaftor in Combination With Ivacaftor for 14 Days
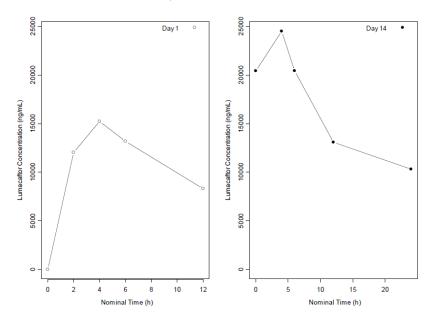

Table 2-1   Summary of Pharmacokinetic Parameters for Lumacaftor and M28-Lumacaftor on Day 1 and Day 14

| | | Day 1 | | | Day 14 | | |
| | | Median (min, max) | Arithmetic Mean (SD) | | Median (min, max) | Arithmetic Mean (SD) | |
Analyte	N	t_{max} (h)	C_{4h} (ng/mL)	C_{12h} (ng/mL)	t_{max} (h)	C_{4h} (ng/mL)	C_{12h} (ng/mL)
LUM	10[a]	4.08 (1.98, 11.13)	15200 (6740)	8320 (3740)	4.08 (0.00, 6.47)	24500 (10400)	13100 (8070)
M28-LUM	10[a]	11.08 (6.42, 11.82)	176 (79.0)	306 (110)	0.00 (0.00, 6.47)	2040 (1230)	1800 (1290)

C_{4h}: concentration at 4 hours; C_{12h}: concentration at 12 hours; LUM: lumacaftor; min: minimum; max: maximum; N: number of observations; PK: pharmacokinetic; SD: standard deviation; t_{max}: time of maximum concentration.

[a]   N = 9 for Day 14 C_{4h} as 1 subject did not have a PK sample drawn at the 4-hour time point on Day 14 and N = 9 for Day 14 C_{12h} as 1 subject did not have a PK sample drawn at the 12 hour time point on Day 14.

Figure 11-5   Mean Ivacaftor Concentration Versus Time Profiles on Day 1 and Day 14 After Administration of Lumacaftor in Combination With Ivacaftor for 14 Days
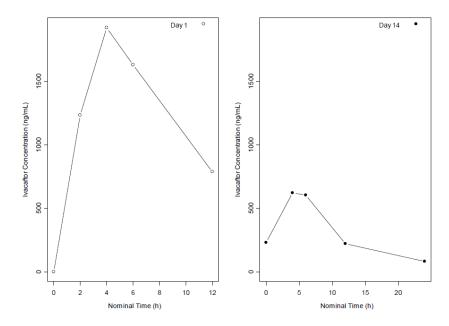

Table 2-2   Summary of Pharmacokinetic Parameters for Ivacaftor, M1-Ivacaftor, and M6-Ivacaftor on Day 1 and Day 14

		Day 1			Day 14		
		Median (min, max)	Arithmetic Mean (SD)		Median (min, max)	Arithmetic Mean (SD)	
Analyte	N	t_{max} (h)	C_{4h} (ng/mL)	C_{12h} (ng/mL)	t_{max} (h)	C_{4h} (ng/mL)	C_{12h} (ng/mL)
IVA	10[a]	4.13	1920	788	4.09	622	222
		(2.08, 6.47)	(727)	(327)	(3.98, 6.47)	(322)	(322)
M1-IVA	10[a]	4.37	3940	1770	4.09	2380	704
		(4.03, 6.47)	(1380)	(447)	(3.98, 6.47)	(1360)	(833)
M6-IVA	10[a]	6.42	1810	2800	4.13	4240	2340
		(5.95, 11.13)	(981)	(1430)	(0.00, 6.47)	(1990)	(895)

C_{4h}: concentration at 4 hours; C_{12h}: concentration at 12 hours; IVA: ivacaftor; min: minimum; max: maximum; N: number of observations; PK: pharmacokinetic; SD: standard deviation; t_{max}: time of maximum concentration.

[a]   N = 9 for Day 14 C_{4h} as 1 subject did not have a PK sample drawn at the 4-hour time point on Day 14 and N = 9 for Day 14 C_{12h} as 1 subject did not have a PK sample drawn at the 12 hour time point on Day 14.

Part B

- The PK Set contained data for 57 subjects.

- Week 16 pre-dose samples from one Subject were excluded from analysis due to the PK samples being taken after the dose was administered.

- Week 16 and Week 24 samples from one Subject and Week 24 samples from another Subject were excluded from analysis due to the PK samples being taken after dose interruptions.

- All PD analyses were conducted using the full analysis set (FAS), which included 58 enrolled subjects who were exposed to any amount of study drug.

Figure 11-11 Mean Lumacaftor Trough Plasma Concentration Profile After
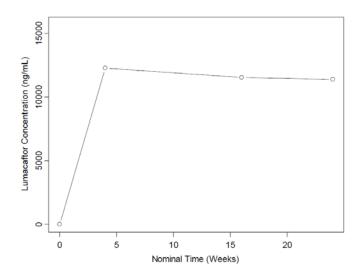Administration of Lumacaftor in Combination With Ivacaftor for
24 Weeks

Table 11-4 Summary of Pharmacokinetic Parameters for Lumacaftor and M28-Lumacaftor

Statistic	Day 1 C_{3-6h} (ng/mL)	Day 15 C_{3-6h} (ng/mL)	Week 4 C_{trough} (ng/mL)	Week 4 C_{3-6h} (ng/mL)	Week 16 C_{trough} (ng/mL)	Week 24 C_{trough} (ng/mL)	$C_{trough,ave}$ (ng/mL)	$C_{3-6h,ave}$ (ng/mL)
				Lumacaftor				
N	57	55	53	54	53	51	55	55
Mean	17100	21400	12300	22000	11500	11400	11800	21700
(SD)	(6260)	(6850)	(6780)	(8470)	(6020)	(5300)	(5700)	(6470)
				M28-Lumacaftor				
N	57	55	53	54	53	51	55	55
Mean	186	1660	1780	1730	1610	1710	1660	1690
(SD)	(96.3)	(843)	(903)	(884)	(859)	(947)	(847)	(831)

Sources: Table 14.4.1.7 and Table 14.4.1.10.
C_{3-6h}: observed concentration at 3 to 6 hours postdose; $C_{3-6h,ave}$: average of individual observed concentration at 3 to 6 hours postdose across Day 15 and
Week 4 Visits; C_{trough}: observed predose concentration; $C_{trough,ave}$: average of individual observed predose concentrations across Week 4 and Week 16
Visits; N: number of observations; SD: standard deviation.

Figure 11-13 Mean Ivacaftor Trough Plasma Concentration Profile After
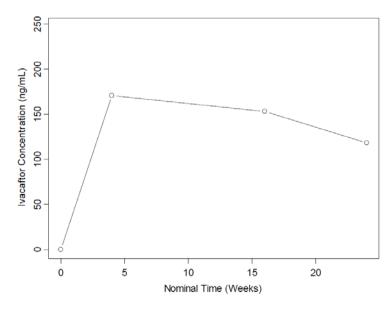Administration of Lumacaftor in Combination With Ivacaftor for
24 Weeks

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Table 11-5   Summary of Pharmacokinetic Parameters for Ivacaftor, M1-Ivacaftor, and M6-Ivacaftor

Statistic	Day 1 C_{3-6h} (ng/mL)	Day 15 C_{3-6h} (ng/mL)	Week 4 C_{trough} (ng/mL)	Week 4 C_{3-6h} (ng/mL)	Week 16 C_{trough} (ng/mL)	Week 24 C_{trough} (ng/mL)	$C_{trough,ave}$ (ng/mL)	$C_{3-6h,ave}$ (ng/mL)
				Ivacaftor				
N	57	55	53	54	52	51	54[a]	55
Mean	1980	751	171	779	153	118	164	765
(SD)	(850)	(433)	(228)	(389)	(150)	(87.2)	(160)	(350)
				M1-Ivacaftor				
N	57	55	53	54	53	51	55	55
Mean	4170	2670	684	2800	690	493	682	2750
(SD)	(1940)	(1330)	(816)	(1410)	(627)	(409)	(577)	(1140)
				M6-Ivacaftor				
N	57	55	53	54	53	51	55	55
Mean	2040	4360	2490	4690	2360	1790	2380	4550
(SD)	(1650)	(2340)	(2150)	(3360)	(1570)	(1180)	(1420)	(2450)

Sources: Table 14.4.1.7 and Table 14.4.1.10.
C_{3-6h}: observed concentration at 3 to 6 hours postdose; $C_{3-6h,ave}$: average of individual observed concentration at 3 to 6 hours postdose across Day 15 and Week 4 Visits; C_{trough}: observed predose concentration; $C_{trough,ave}$: average of individual observed predose concentrations across Week 4 and Week 16 Visits; N: number of observations; SD: standard deviation.
[a]   Number of subjects with PK data for $C_{trough,ave}$ was 54 subjects as 1 subject did not have an IVA $C_{trough,ave}$ result (the subject's predose PK sample at Week 4 was not taken, and the predose IVA result at Week 16 was below the limit of quantification).

Summary of LUM and IVA Exposures in Subjects with CF Who Are 6 Years of Age and Older

		LUM AUC0-12h (hr·µg/mL)	IVA AUC0-12h (hr·µg/mL)
Age Group	N	Mean (SD)	Mean (SD)
6 through 11 years	62	203 (57.4)	5.26 (3.08)
12 through 17 years	98	241 (61.4)	3.90 (1.56)
18 years and older	265	216 (47.9)	3.80 (1.94)

1. AUC0-12h: area under the concentration-time curve from 0 to12 hours; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetics; SD: standard deviation; q12h: every 12 hours

2. Note: PK data are from Study 011 Part B (subjects 6 through 11 years of age) and Studies 103 and 104 (12 through 17 years of age; 18 years of age and older). Subjects in Study 011 received LUM 200 mg/IVA 250 mg q12h for 24 weeks and subjects in Studies 103 and 104 received LUM 400 mg/IVA 250 mg q12h for 24 weeks.

> *Rapporteur's Comments*
>
> *It is agreed that the concentrations of lumacaftor (LUM) following a LUM 100 mg/IVA 125-mg FDC tablet q12h in Subjects 6 through 11 Years of Age with Cystic Fibrosis (Part B) appear comparable to concentrations in observed in adolescents and adult subjects with cystic fibrosis administered LUM 400 mg q12h/IVA 250 mg q12h. For ivacaftor (IVA) steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104.*
>
> *Similar to previous studies, decreases in the levels of IVA due to induction by LUM were observed.*
>
> *It is recommended to pool these data with the data from other studies into a population PK model in order to support a line extension.*

PHARMACODYNAMIC EVALUATION - Part B only

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Sweat Chloride

A reductions in sweat chloride was seen as early as Day 15, i.e., -19.7 mmol/L (P<0.0001), and seemed to sustain through Week 24, i.e., -24.8 mmol/L (P<0.0001). Following a 2-week Washout Period, there was a complete reversal at Week 26, i.e., -3.1 (10.4) mmol/L.
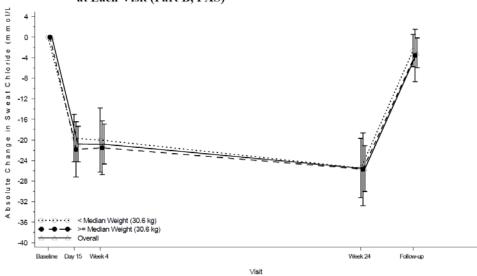
Figure 11-21 Summary Statistics of Absolute Change From Baseline in Sweat Chloride at Each Visit (Part B, FAS)

Nutritional Status

Increases in BMI and weight were seen as early as Day 15 and continued through the study period. The mean absolute change from baseline at Week 24 was 0.64 kg/m2 (P<0.0001) for BMI and 0.15 (P<0.0001) for BMI-for-age z-score. The mean absolute change from baseline at Week 24 was 2.6 kg (P<0.0001) for weight and 0.13 (P<0.0001) for weight-for-age z-score.

Increases in height were seen at Week 24, i.e., 2.9 cm (P<0.0001) for height and 0.03 (P = 0.2249) for height-for-age z-score.

The mean (SD) absolute changes from baseline at the Week 26 Safety Follow-up Visit were 0.58 (0.66) kg/m2 (BMI), 0.11 (0.28) (BMI-for-age z-score), 2.6 (1.5) kg (weight), 0.11 (0.22) (weight-for-age z-score), 3.2 (1.3) cm (height), and 0.05 (0.19) (height-for-age z-score).
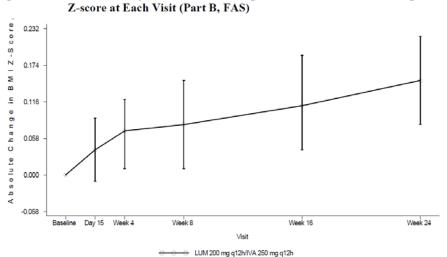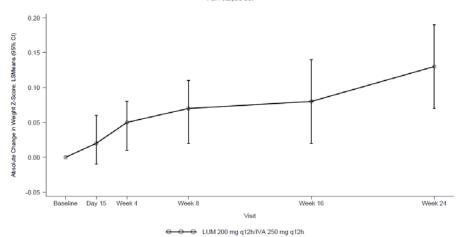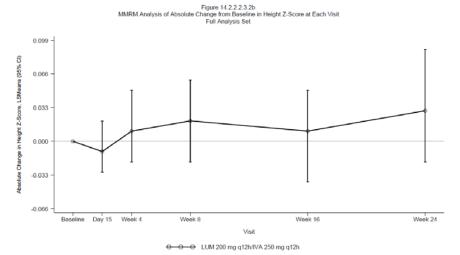
Figure 11-23 MMRM Analysis of Absolute Change From Baseline in BMI-for-age Z-score at Each Visit (Part B, FAS)

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Figure 14.2.2.2.2.2b
MMRM Analysis of Absolute Change from Baseline in Weight Z-Score at Each Visit
Full Analysis Set

Figure 14.2.2.2.2.3.2b
MMRM Analysis of Absolute Change from Baseline in Height Z-Score at Each Visit
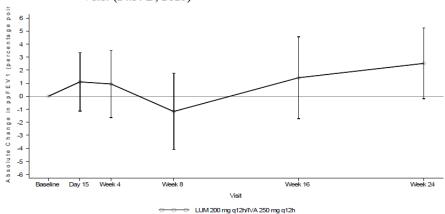Full Analysis Set

Respiratory Effects

An improvement in ppFEV1 was seen at Week 24, i.e., 2.5 percentage points (P = 0.0671). Following the 2-week Washout Period, ppFEV1 values returned to baseline, i.e., the mean absolute change from Week 24 to Week 26 was -3.2 percentage points (P = 0.0003).

Figure 11-24 MMRM Analysis of Absolute Change From Baseline in ppFEV$_1$ at Each Visit (Part B, FAS)

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A favourable change in the CFQ-R respiratory domain score was seen at Week 24, i.e., 5.4 points (P = 0.0085).

A favorable trend for changes in the TSQM domains was seen at Week 24, i.e., 9.2 points (P = 0.0005) for the effectiveness domain, -0.3 points (P = 0.5270) for the side effects domain, 11.1 points (P<0.0001) for the convenience domain, and 3.6 points (P = 0.2018) for the global satisfaction domain.

Exploratory LCI Substudy

A reduction in LCI was seen as early as Day 15, i.e., -0.97 (P = 0.0002), and sustained through Week 24, i.e., -0.88 (P = 0.0018), and after the 2-week Washout Period, i.e., -0.80.

Figure 11-25 MMRM Analysis of Absolute Change From Baseline in LCI$_{2.5}$ at Each Visit (Part B, LCI Substudy Set)

Rapporteur's Comments

Although the PD effects observed seem to be consistent with the observed PD effects of LUM/IVA in older populations for most parameters, given a single-arm study design, it is not possible to exclude effects from bias, i.e., Hawthorne effect during data collection from questionnaire, bias from other adjunctive therapies, or bias from natural growth. However, the complete reversal of sweat chloride following a two-week washout period is considered to be more robust evidence. Further, the clinical relevance of the observed change from baseline in secondary endpoints should be discussed in detail. The Applicant should also clarify the observed "deterioration" in ppFEV1 at Week 8.

SAFETY EVALUATION

Safety Results

Part A

No deaths, other serious AEs (SAEs), or AEs leading to premature treatment discontinuation occurred during Part A.

Overall, the most common AEs were cough (4 [40.0%] subjects) and headache (3 [30.0%] subjects).

There were no clinically meaningful results or clinically significant abnormalities in hematology and coagulation studies, urinalysis, vital signs, height, weight, BMI, or ECGs.

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A few subjects had <3 × upper limit of normal (ULN) elevations in alanine aminotransferase (ALT) on Day 7 or Day 14. None of these elevations were associated with an increase in bilirubin. There was 1 clinically significant hepatic enzyme increase but was considered not related to study drug.

While declines in ppFEV1 were noted in 9 of 10 subjects 4 hours post-dose (mean [standard deviation]) absolute change in ppFEV1 of 10.07 [10.290] percentage points), the mean ppFEV1 returned to near baseline by Day 7 and was approximately 3 percentage points above baseline at the Safety Follow-up Visit. A similar pattern was observed for percent predicted forced vital capacity (ppFVC) and percent predicted forced expiratory flow (ppFEF25%-75%). There was one AE of forced expiratory volume decreased was moderate in severity, it was considered not related to study. The etiology of the declines in ppFEV1 is unclear. The temporal nature (onset within 4 hours of dosing and resolution by Day 7) suggests airway narrowing (bronchoconstriction).

Part B

A total of 55 (94.8%) subjects had at least 1 AE.

• The most common AEs (≥15%), mostly expected manifestations of CF disease:

   o   Cough (29 [50.0%] subjects),

   o   Nasal congestion (12 [20.7%] subjects),

   o   Infective pulmonary exacerbation of CF (12 [20.7%] subjects),

   o   Headache (12 [20.7%] subjects).

   o   Six (10.3%) subjects had AEs leading to treatment interruption.

• The majority of AEs were mild or moderate in severity (mild: 22 [37.9%] subjects and moderate: 29 [50.0%] subjects). No life-threatening AEs occurred.

• A total of 20 (34.5%) subjects had at least 1 AE considered related or possibly related to study drug.

• Two (3.4%) subjects had AEs that led to treatment discontinuation

   o   ALT increased and AST increased in 1 [1.7%] subject

   o   Urticaria in 1 [1.7%] subject.

• A total of 4 (6.9%) subjects had SAEs

   o   2 [3.4%] subjects had SAEs of infective pulmonary exacerbation of CF that were considered not related or unlikely related to study drug,

   o   1 [1.7%] subject had an SAE of ileus that was considered unlikely related to study drug,

   o   1 [1.7%] subject had SAEs of ALT increased and AST increased that were considered possibly related to study drug (see below).

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Table 12-9   Related Adverse Events With a Frequency of ≥5% at the Preferred Term Level by System Organ Class and Preferred Term (Part B, Safety Set)

System Organ Class Preferred Term[b]	n (%)[a]		
	< Median Weight N = 28	≥ Median Weight N = 30	Overall N = 58
Subjects with any AEs			
Related	2 (7.1)	0	2 (3.4)
Possibly related	5 (17.9)	13 (43.3)	18 (31.0)
Respiratory, thoracic, and mediastinal disorders			
Cough			
Related	0	0	0
Possibly related	1 (3.6)	4 (13.3)	5 (8.6)
Sputum increased			
Related	0	0	0
Possibly related	1 (3.6)	4 (13.3)	5 (8.6)
Gastrointestinal disorders			
Constipation			
Related	0	0	0
Possibly related	0	2 (6.7)	2 (3.4)
Investigations			
Alanine aminotransferase increased			
Related	1 (3.6)	0	1 (1.7)
Possibly related	0	4 (13.3)	4 (6.9)
Aspartate aminotransferase increased			
Related	1 (3.6)	0	1 (1.7)
Possibly related	0	3 (10.0)	3 (5.2)

Table 12-10   Summary of AESIs by Preferred Term (Part B, Safety Set)

AESI Preferred Term[b]	n (%)[a]		
	< Median Weight N = 28	≥ Median Weight N = 30	Overall N = 58
Subjects with any AESIs	5 (17.9)	6 (20.0)	11 (19.0)
AESI of elevated transaminases	2 (7.1)	5 (16.7)	7 (12.1)
Alanine aminotransferase increased	2 (7.1)	5 (16.7)	7 (12.1)
Aspartate aminotransferase increased	1 (3.6)	3 (10.0)	4 (6.9)
AESI of respiratory symptoms	1 (3.6)	1 (3.3)	2 (3.4)
Dyspnoea	1 (3.6)	0	1 (1.7)
Respiration abnormal	0	1 (3.3)	1 (1.7)
AESI of respiratory events	3 (10.7)	1 (3.3)	4 (6.9)
Dyspnoea	1 (3.6)	0	1 (1.7)
Respiration abnormal	0	1 (3.3)	1 (1.7)
Wheezing	2 (7.1)	0	2 (3.4)

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Subject Identification	Death	Other Serious Adverse Event	Discontinuation Due to Adverse Event	Other Significant Adverse Events	Elevated Liver Function Tests[a]	Pregnancy[b]
					X	
		X				
		X			X	
		X				
					X	
				X		
			X		X	
					X	
			X			
		X				

Note: All subjects with a narrative should be listed in this table. For subjects with events in multiple columns, the narrative is provided in leftmost applicable category.

[a] Defined as alanine aminotransferase and/or aspartate aminotransferase >5 × ULN. Some elevated liver function tests may not have been considered by the investigator to be an adverse event.

[b] Pregnancy is not considered an adverse event.

Hepatic Events

- A total of 7 (12.1%) subjects had AESIs of elevated transaminases.

    o Case: SAE, possibly related to study drug; IMP resumed.

    o Case: re-elevation of AST/ALT after resumption of IMP; hence related to study drug and treatment withdrawn.

    o Case: possibly related to study drug; drug never resumed.

- The overall incidence of maximum on-treatment liver enzyme elevations (ALT or AST) was 19.3% for >3 ×ULN, 8.8% for >5 × ULN, and 5.3% for >8 × ULN.

Observed ALT or AST	> 3X ULN	> 5X ULN	> 8X ULN
Study 011 Part B	19.3%	8.8%	5.3%
SPC Section 4.8 lumacaftor/ivacaftor	5.2%	2.0%	0.8%
SPC Section 4.8 placebo	5.1%	1.9%	0.5%

- No subjects had elevations in total bilirubin. The hepatitis profile was negative.

Respiratory Events

A total of 4 (6.9%) subjects had AESIs of respiratory events.

- 2 (3.4%) subjects with AESIs of respiratory symptoms (dyspnea and respiration abnormal)
- 2 (3.4%) subjects with AESIs of other respiratory events (wheezing).
- All respiratory AESIs were mild in severity and none were considered serious or required interruption or discontinuation of study drug treatment.

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Cardiovascular Events

- There was substantial variability in BP measurements during the 24-week Treatment Period.

- The mean change from baseline at Week 24 was 3.0 mm Hg in systolic BP and 0.8 mm Hg in diastolic BP.

- No subjects had an AE related to BP increased or hypertension.

There were no clinically meaningful trends identified from serum chemistry, hematology, coagulation studies, urinalysis, pulse oximetry, ECG, spirometry, or ophthalmological examination results.

Rapporteur's Comments

The study report stating, in Part B, "The most common AEs (≥15%) by PT were cough (29 [50.0%] subjects), nasal congestion (12 [20.7%] subjects), infective pulmonary exacerbation of CF (12 [20.7%] subjects), and headache (12 [20.7%] subjects). These AEs were mostly expected manifestations of CF disease." should be clarified, i.e., whether they are related to the IMP or not. As according to guidance CT1 section 2.3. (32.), CT3 sections 7.2.3.1. and 7.2.3.2., AEs should be categorised as expected vs. unexpected to the IMP by the nature or severity of which not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)' and an increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Although LUM 100 mg/IVA 125-mg FDC tablet q12h seems to be well tolerated in subjects aged 6 through 11 years with CF, there are serious safety concerns, especially on the hepatic events:

- Given Part B designed to capture potential adverse reactions, i.e., a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%, the observed 7 (12.1%) subjects with elevated transaminases (AST or ALT >5x ULN) in the study suggest a significant incidence of hepatic injury.

- The rates of observed AST or ALT >3x ULN or above are much higher than those described in the SPC, i.e., clinical studies with 24 weeks of treatment with lumacaftor/ivacaftor in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The study report also states "Although the incidences of transaminases elevations (ALT or AST) appeared to be higher than that observed in subjects aged 12 years and older (Studies VX12-809-103 and VX12-809-104), these are generally consistent with observations in subjects of the same age group from previously completed placebo-controlled IVA monotherapy studies and the information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults." Given that ivacaftor (IVA) steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104, the observed higher incidence of transaminases elevations seems to be relevant. Further, according to Flass T, J Cyst Fibros 2013 Mar;12(2):116-24 and Woodruff SA, J Cyst Fibros 2016 Aug 20. pii: S1569-1993(16)30571-9, among 298 children with CF born in Colorado from 1982 to 2005, of which 80.5% were identified by newborn screen, a small number of AST/ALT >3x ULN generally occurred during the first 2 years of life; none of which occurred at an annual visit beyond 2 years of age. Persistent elevations of AST, ALT or GGT more than 3 times the upper limit of normal were very rare. Therefore, the statement "transaminase elevations are more common in younger patients with CF than in adults" for rationalizing the observed elevated AST/ALT cannot be agreed.

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- The reported Case had re-elevation of AST/ALT after resumption of LUM/IVA and hence the treatment was withdrawn. The causal relationship suggests a drug-induced liver injury.

- Given the SAE of Case was considered to be possibly related to study drug, the Applicant should clarify whether the SAE was an expected adverse event as per Investigator's brochures, or a Suspected Unexpected Serious Adverse Reactions (SUSAR) report had been submitted.

The statement, "The overall data acquired to-date does not suggest an association between IVA treatment and cataract development" is contradictory to "a potential association has not been fully excluded" and should be deleted, given an adverse event of cataract considered by the investigator to be possibly related to study drug and the juvenile rat toxicity study demonstrating lens opacities in some animals.

The Statistical Analysis Plan Part B states "One unplanned interim analysis (IA) was conducted after all subjects completed Week 4, with a data snapshot date of 19 June 2015." and "The DMC conducted one review of the study safety data, with the same data snapshot date as the one used for the interim analysis." The Applicant should provide the minutes from the IDMC.

2.1.1. Discussion on clinical aspects

Design

The study design is not considered to be in line with the guidance for children with CF EMEA/CHMP/EWP/9147/2008-corr*. The study titled as "Phase 3" did not reflect correctly with the study objectives since none of the study objectives were subjected to confirmatory testing.

Given that both Parts were single-arm, it is difficult to scrutinize the observed PD effects. The Applicant did not discuss the clinical relevance of the observed PD effects. It is not clear why the study allowed patients who have completed Part A to continue Part B and patients with transaminase levels as high as 5x ULN to be included in Part B without the safety profile in the target population being defined at that time. Further, it is not clear why Part B included in the PIP before initiation.

Pharmacokinetics

The concentrations of lumacaftor (LUM) following a LUM 100 mg/IVA 125-mg FDC tablet q12h in Subjects 6 through 11 Years of Age with Cystic Fibrosis (Part B) appear comparable to concentrations in observed in adolescents and adult subjects with cystic fibrosis administered LUM 400 mg q12h/IVA 250 mg q12h. The ivacaftor (IVA) steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104.

Similar to previous studies, decreases in the levels of IVA due to induction by LUM were observed.

It is recommended to pool these data with the data from other studies into a population PK model in order to support a line extension.

Pharmacodynamics

Although the PD effects observed seem to be consistent with those from previous studies, the clinical relevance of the observed change from baseline have not been discussed in detail. Given a single-arm design, it is not possible to exclude effects from potential bias. However, the complete reversal of sweat chloride following a two-week washout period seems to be robust. There is a lack of full explanation on the deterioration in ppFEV1 at Week 8.

Although LUM 100 mg/IVA 125-mg FDC tablet q12h seems to be well tolerated in subjects aged 6 through 11 years with CF, there are serious safety concerns, especially on the hepatic events:

- Given Part B designed to capture adverse reactions, i.e., a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%, the observed 7 (12.1%) subjects with elevated transaminases (AST or ALT >5x ULN) suggest a significant incidence of hepatic injury.

- The rates of observed AST or ALT >3x ULN or above are much higher than those described in the SPC, i.e., clinical studies with 24 weeks of treatment with lumacaftor/ivacaftor in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The study report also states "Although the incidences of transaminases elevations (ALT or AST) appeared to be higher than that observed in subjects aged 12 years and older (Studies VX12-809-103 and VX12-809-104), these are generally consistent with observations in subjects of the same age group from previously completed placebo-controlled IVA monotherapy studies and the information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults." Given that ivacaftor steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104, the observed higher incidence of transaminases elevations seems to be relevant to IVA. Further, according literature, persistent elevations of AST, ALT or GGT more than 3 times the upper limit of normal in children aged > 2 years with CF were very rare. Therefore, the statement "transaminase elevations are more common in younger patients with CF than in adults" for rationalizing the observed elevated AST/ALT cannot be agreed.

- The reported Case had re-elevation of AST/ALT after resumption of LUM/IVA and hence the treatment was withdrawn. The causal relationship suggests a drug-induced liver injury.

- Given the SAE of Case was considered to be possibly related to study drug, the Applicant should clarify whether the SAE was an expected adverse event as per Investigator's brochures, otherwise a Suspected Unexpected Serious Adverse Reactions (SUSAR) report should have been submitted.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Data from Study VX13-809-011 (Study 011) suggest potential drug-induced liver injury in subjects aged 6 through 11 years with CF and higher ivacaftor (IVA) steady state levels. These findings should be re-assessed along with results from Study VX14-809-109 (Study 109) and Study VX14-809-110 (Study 110) when available. The risk-benefit assessment in subjects aged 6 through 11 years with CF is hence unable to be determined.

Recommendation

Depending on the Applicant's response, further action may be required.

Additional clarifications requested

1. The clinical relevance of the observed change from baseline in secondary endpoints should be discussed in detail.

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2. The Applicant should provide a full explanation on the deterioration in ppFEV1 at Week 8.

3. The study report stating, in Part B, The most common AEs (≥15%) by PT were cough (29 [50.0%] subjects), nasal congestion (12 [20.7%] subjects), infective pulmonary exacerbation of CF (12 [20.7%] subjects), and headache (12 [20.7%] subjects). These AEs were mostly expected manifestations of CF disease." should be clarified, i.e., whether they are related to the IMP or not. As according to guidance CT1 section 2.3. (32.), CT3 sections 7.2.3.1. and 7.2.3.2., AEs should be categorised as expected vs. unexpected to the IMP by the nature or severity of which not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)' and an increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

4. The Applicant is required to address the following comments based on the data provided: Although LUM 100 mg/IVA 125-mg FDC tablet q12h seems to be well tolerated in subjects aged 6 through 11 years with CF, there are serious safety concerns, especially on the hepatic events:

- Given Part B designed to capture adverse reactions, i.e., a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%, the observed 7 (12.1%) subjects with elevated transaminases (AST or ALT >5x ULN) suggest a significant incidence of hepatic injury.

- The rates of observed AST or ALT >3x ULN or above are much higher than those described in the SPC, i.e., clinical studies with 24 weeks of treatment with lumacaftor/ivacaftor in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The study report also states "Although the incidences of transaminases elevations (ALT or AST) appeared to be higher than that observed in subjects aged 12 years and older (Studies VX12-809-103 and VX12-809-104), these are generally consistent with observations in subjects of the same age group from previously completed placebo-controlled IVA monotherapy studies and the information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults." Given that ivacaftor steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104, the observed higher incidence of transaminases elevations seems to be relevant to IVA. Further, according literature, persistent elevations of AST, ALT or GGT more than 3 times the upper limit of normal in children aged >2 years with CF were very rare. Therefore, the statement "transaminase elevations are more common in younger patients with CF than in adults" for rationalizing the observed elevated AST/ALT cannot be agreed.

- The reported Case had re-elevation of AST/ALT after resumption of LUM/IVA and hence the treatment was withdrawn. The causal relationship suggests a drug-induced liver injury.

And the Applicant is required to provide the following information:

1) Comparing above liver events with similar events in adults and adolescents [including any safety paediatric reports received by the company and any included in the Periodic Safety Update Reports (PSURs)].

2) Comparing above liver events with those in pivotal studies, i.e., Study VX14-809-109 and Study VX15-809-110 from minutes of IDMC and Development Safety Update Reports (DSURs).

3) Implications for the SmPC, PIL, and future paediatric studies, and proposal for amendments with justification.

5. Given the SAE of Case was considered to be possibly related to study drug, the Applicant should clarify whether the SAE was an expected adverse event as per Investigator's brochures, or a Suspected Unexpected Serious Adverse Reactions (SUSAR) report had been submitted.

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6. The statement, "The overall data acquired to-date does not suggest an association between IVA treatment and cataract development" is contradictory to "a potential association has not been fully excluded" and should be deleted, given an adverse event of cataract considered by the investigator to be possibly related to study drug and the juvenile rat toxicity study demonstrating lens opacities in some animals.

7. The Statistical Analysis Plan Part B states "One unplanned interim analysis (IA) was conducted after all subjects completed Week 4, with a data snapshot date of 19 June 2015." and "The DMC conducted one review of the study safety data, with the same data snapshot date as the one used for the interim analysis." The Applicant should provide the minutes from the IDMC.

8. The Applicant is requested to present the results for the secondary endpoints as well as the characteristics of the patients before and after the unplanned interim analysis to provide reassurance that the integrity of the trial has not been compromised.

9. The Applicant is requested to present analysis for sweat chloride where the worst value is used instead of the median values, when replicate values are available.

10. The Applicant is requested to justify why change from baseline to Day 15 and Week 4 was calculated using the average of Day 15 and Week 4 for sweat chloride.

11. There were seven subjects with important protocol violations. The Applicant is requested to assess the impact of these violations on the assessment of secondary endpoints.

4. Assessment of the responses to the request for supplementary information No. 1

Clinical aspects

Question 1

The clinical relevance of the observed change from baseline in secondary endpoints should be discussed in detail.

Summary of the MAH's response

Sweat chloride

Sweat chloride is an in vivo measure of CFTR function; therefore a reduction in sweat chloride indicates an improvement in CFTR function. Data from natural history indicate that improving CFTR function in patients homozygous for *F508del* by 10% to 20% would result in meaningful clinical benefit.

In Study 011, treatment with LUM/IVA resulted in a reduction in sweat chloride at Day 15 and at Week 4 that was sustained through Week 24. The within-group least squares (LS) mean absolute change from baseline was -19.7 mmol/L (*P*<0.0001) for the average at Day 15 and at Week 4 and -24.8 mmol/L (*P*<0.0001) at Week 24, reflecting an improvement of approximately 20% in the dysfunctional F508del-CFTR protein. Assessment of sweat chloride at Week 26 Safety Follow-up Visit, following a 2-week Washout, demonstrated nearly complete reversal of the changes in sweat chloride.

After re-initiation of LUM/IVA by Study 011B subjects in Study 110, the mean (SD) absolute change from baseline in sweat chloride was -28.9 (12.3) mmol/L on Day 15, was generally stable during the Treatment Period, and was -29.0 (15.7) mmol/L at Week 24.

Nutritional Status (Measured as Weight and BMI)

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Malnutrition is common in patients with CF because of fat malabsorption and increased energy expenditures due to lung disease. Improved nutritional status, defined as an increase in body mass index (BMI) and/or weight, is considered an appropriate endpoint for therapies targeting pancreatic insufficiency and therapies targeting CF lung disease.

In Study 011B, treatment with LUM/IVA resulted in improvements in measures of nutritional status (BMI and weight and associated z-scores) as early as Day 15 and continued to improve through all visits up to Week 24. The within-group LS mean absolute change from baseline at Week 24 was 0.64 kg/m2 (P<0.0001) for BMI, 0.15 (P<0.0001) for BMI-for-age z-score, 2.6 kg (P<0.0001) for weight, and 0.13 (P<0.0001) for weight-for-age z-score.

Mean BMI remained stable during the 2-week Washout Period between treatment in Study 011B and Study 110. After re-initiation of LUM/IVA administration in Study 110, the mean (SD) change from baseline in BMI was 0.63 (0.65) kg/m2 on Day 15, showed a general trend of increase, and was 1.17 (1.13) kg/m2 at Week 36. Mean BMI-for-age z-score generally remained stable during the 2-week Washout Period and in Study 110. A similar pattern was observed for weight and weight-for-age z-score.

Patient-reported Outcomes

The CFQ-R measures quality-of-life domains, including respiratory symptoms, digestive symptoms, emotion, and health perception. The TSQM encompasses measures of effectiveness, side effects, convenience, and global satisfaction, and is a widely used measure of satisfaction with medication.

In Study 011B, treatment with LUM/IVA resulted in a favourable change in the CFQ-R respiratory domain score (Version: Children Ages 6 to 11) at Week 24. The within-group LS mean absolute change from baseline in the CFQ-R respiratory domain score at Week 24 was 5.4 points (P = 0.0085). Treatment with LUM/IVA also resulted in a favourable trend for changes in the TSQM domains at Week 24. The within-group LS mean absolute change from baseline at Week 24 was 3.6 points (P = 0.2018) for the global satisfaction domain.

Lung Function (Spirometry and LCI)

Forced expiratory volume in 1 second (FEV1) is linked to mortality, thus, any significant difference between placebo and active treatment is potentially clinically relevant. LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques that has been evaluated in patients as young as infants. LCI correlates with FEV1 in its ability to measure airway disease and can detect lung disease at an earlier stage than spirometry. Effect sizes in studies have ranged from -1 to -2 depending on the type of intervention and the duration of treatment. Overall, an improvement in LCI indicates an improvement in the ventilation inhomogeneity that is characteristic of CF lung disease and thus has the potential for long-term benefit, including impacting the progressive and irreversible loss of lung function that is the major cause of morbidity and mortality in patients with CF.

Given the potential advantages of a more sensitive measurement of early airway disease in younger children, LCI was assessed as an exploratory endpoint in Study 011B. LCI2.5 (the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value) is the most commonly used multiple-breath washout parameter. LCI5.0 (the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value) was also assessed as an exploratory endpoint.

In Study 011B, subjects had a mean (SD) baseline ppFEV1 of 91.4 (13.7) and a mean (SD) baseline LCI2.5 of 9.99 (2.67), demonstrating that CF subjects with normal ppFEV1 values still have significant CF lung disease. Treatment with LUM/IVA demonstrated an improvement (reduction) in LCI2.5 as early as Day 15 that was sustained through Week 24. The within-group LS mean absolute change from

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baseline in LCI2.5 was -0.86 (P = 0.0007) at Day 15, -0.88 (P = 0.0018) at Week 24, and -0.94 (P = 0.0002) through Week 24. A similar trend was observed for LCI5.0. Consistent with the finding that improvements in LCI are correlated to changes in FEV1, treatment with LUM/IVA also resulted in an improvement in ppFEV1 at Week 24. The magnitude of the improvement in ppFEV1 in Study 011B was consistent with the statistically significant improvements in ppFEV1 that were rapid and sustained across all visits during the 24-week Treatment Period in studies in subjects 12 years of age and older. At the Week 26 Safety Follow-up Visit, following the 2-week Washout Period, ppFEV1 values returned to baseline, providing confidence that the improvement during the 24-week Treatment Period was treatment related. Mean LCI2.5 generally remained stable during the 2-week Washout Period between treatments in Study 011B. The LS mean treatment difference was -1.22 (P<0.0001) for the absolute change in LCI2.5 at Week 24 and 3.0 percentage points (P = 0.0195) for the absolute change in ppFEV1 at Week 24.

In summary, results from Study 011B demonstrated that treatment with LUM/IVA resulted in rapid and sustained effects on multiple PD endpoints of CFTR modulation in multiple organ systems over 24 weeks of treatment, supporting the clinical relevance of the changes. These changes include improvements in sweat chloride, nutritional status (BMI and weight and associated z-scores), and lung function (spirometry and LCI). There are no established minimum clinically important differences for these endpoints; however, the changes observed in Study 011B demonstrate a consistent, multi-system impact of CFTR modulation in a population of subjects with severe disease.

Assessment of the MAH's response

Although there are no established minimum clinically important differences for the secondary endpoints, it can be agreed that the observed effects are corroborative to the drug mechanism and pathophysiology of CF and therefore could be beneficial in the target population. The point is considered resolved.

Question 2

The Applicant should provide a full explanation on the deterioration in ppFEV1 at Week 8.

Summary of the MAH's response

The decline in ppFEV1 noted at Week 8 of Study 011B likely represents the intrinsic variability of FEV1 measurements, rather than a genuine clinically relevant event. This is particularly likely given that the mean ppFEV1 change from baseline was greater than zero at all other time points where it was assessed, including Weeks 16 and 24. The decline is not considered a significant safety concern because it resolved while administration of LUM/IVA continued and was generally not associated with clinical manifestations. There were no increases in pulmonary exacerbations (PExs), respiratory adverse events of special interest (AESIs), or other clinically meaningful findings at Week 8.

Assessment of the MAH's response

The explanation on the deterioration in ppFEV1 at Week 8 is not satisfactory. If the decline in ppFEV1 measurement at Week 8 of Study 011B is considered to be attributed to an intrinsic variability in FEV1 measurements, the MAH should investigate further by auditing. **<u>The point is not considered resolved.</u>**

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Question 3

The study report stating, in Part B, The most common AEs (≥15%) by PT were cough (29 [50.0%] subjects), nasal congestion (12 [20.7%] subjects), infective pulmonary exacerbation of CF (12 [20.7%] subjects), and headache (12 [20.7%] subjects). These AEs were mostly expected manifestations of CF disease." should be clarified, i.e., whether they are related to the IMP or not. As according to guidance CT1 section 2.3. (32.), CT3 sections 7.2.3.1. and 7.2.3.2., AEs should be categorised as expected vs. unexpected to the IMP by the nature or severity of which not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)' and an increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Summary of the MAH's response

The MAH clarified that the above AEs are "typical" manifestations in patients with CF. The term "expected" does not refer to the expectedness assessment of AEs according to the reference safety information for expedited reporting purposes. Given these AEs are common manifestations in patients with CF and Study 011B was an open-label study enrolling a relatively small number of subjects, the ability to establish an association between these AEs and LUM/IVA treatment is limited.

Assessment of the MAH's response

The Applicant clarifies that the term "expected" does not refer to the expectedness assessment of AEs based on the Reference Safety Information (RSI); however, the above AEs are consistent with those described in the RSI of the Investigator's Brochure (IB) which the MAH quoted in the response to Question No. 5:

Table 8-1   Incidence of Adverse Drug Reactions: AEs in ≥5% of Subjects Receiving LUM/IVA Combination Therapy and 1% Greater Than Placebo by PT

Adverse Reaction (Preferred Term)	LUM/IVA N = 738 (%)	Placebo N = 370 (%)
Dyspnea	103 (14.0)	29 (7.8)
Diarrhea	81 (11.0)	31 (8.4)
Nausea	75 (10.2)	28 (7.6)
Respiration abnormal	72 (9.8)	22 (5.9)
Oropharyngeal pain	68 (9.2)	30 (8.1)
Upper respiratory tract infection	61 (8.3)	20 (5.4)
Rhinitis	46 (6.2)	18 (4.9)
Flatulence	44 (6.0)	11 (3.0)
Rash	41 (5.6)	7 (1.9)
Rhinorrhea	38 (5.1)	15 (4.1)
Vomiting	37 (5.0)	11 (3.0)

IVA: ivacaftor; LUM: lumacaftor; PT: preferred term

It is acknowledged that Study 011B was a study enrolling a relatively small number of subjects. Given an open-label nature without a control group of the study, adhering to the RSI for determining expectedness of AEs is crucial. The response above is therefore not considered satisfactory. **The point is not resolved.**

Question 4

The Applicant is required to address the following comments based on the data provided: Although LUM 100 mg/IVA 125-mg FDC tablet q12h seems to be well tolerated in subjects aged 6 through 11 years with CF, there are serious safety concerns, especially on the hepatic events:

- Given Part B designed to capture adverse reactions, i.e., a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%, the observed 7 (12.1%) subjects with elevated transaminases (AST or ALT >5x ULN) suggest a significant incidence of hepatic injury.

- The rates of observed AST or ALT >3x ULN or above are much higher than those described in the SPC, i.e., clinical studies with 24 weeks of treatment with lumacaftor/ivacaftor in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The study report also states "Although the incidences of transaminases elevations (ALT or AST) appeared to be higher than that observed in subjects aged 12 years and older (Studies VX12-809-103 and VX12-809-104), these are generally consistent with observations in subjects of the same age group from previously completed placebo-controlled IVA monotherapy studies and the information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults." Given that ivacaftor steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104, the observed higher incidence of transaminases elevations seems to be relevant to IVA. Further, according literature, persistent elevations of AST, ALT or GGT more than 3 times the upper limit of normal in children aged >2 years with CF were very rare. Therefore, the statement "transaminase elevations are more common in younger patients with CF than in adults" for rationalizing the observed elevated AST/ALT cannot be agreed.

- The reported Case had re-elevation of AST/ALT after resumption of LUM/IVA and hence the treatment was withdrawn. The causal relationship suggests a drug-induced liver injury.

And the Applicant is required to provide the following information:

1) Comparing above liver events with similar events in adults and adolescents [including any safety paediatric reports received by the company and any included in the Periodic Safety Update Reports (PSURs)].

2) Comparing above liver events with those in pivotal studies, i.e., Study VX14-809-109 and Study VX15-809-110 from minutes of IDMC and Development Safety Update Reports (DSURs).

3) Implications for the SmPC, PIL, and future paediatric studies, and proposal for amendments with justification.

Summary of the MAH's response

To further evaluate the data related to liver function tests (LFTs) in subjects aged 6 through 11 years who were treated with LUM/IVA, analyses of clinical data across studies with varying age groups were conducted. Data of Study 109 and an interim report from Study 110 were used rather than data from a Data Monitoring Committee (DMC). Findings:

1) The background incidence rate of transaminase elevations and similar AEs was more common in subjects with CF, aged 6 through 11 years, than in subjects with CF, aged 12 years or older.

2) In subjects aged 6 through 11 years, the overall incidence rate of transaminase elevations and similar AEs that occurred during LUM/IVA treatment was similar to the background (placebo) incidence rate of this same population.

3) In subjects aged 6 through 11 years, all LFT abnormalities had isolated transaminase elevations

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without concurrent elevations in total bilirubin.

Background Incidence Rates by Age Group

In the CF population aged 6 through 11 years, the background incidence rate of transaminase elevations was determined based on *placebo data from 24-week Study 109 and the first 24 weeks of Study 770-103* (Phase 3 placebo-controlled IVA monotherapy study in subjects aged 6 through 11 years with CF and the *G551D* mutation that is provided here for comparison of LFT data in the CF population). The placebo group in Study 109 had incidence rates of AST/ALT elevations above threshold (i.e., 3 ×, 5 ×, and 8 × ULN) that were 7.9%, 3.0%, and 2.0%, respectively (Table 2) whereas the placebo group in Study 770-103 had incidence rates of 15.4%, 3.8%, and 0%, respectively. Together, the data from these studies suggest elevated transaminases are common background events in the CF population aged 6 through 11 years.

In the CF population aged 12 years and older, the background incidence rate of transaminase elevations was determined based on the pooled placebo data from two 24-week studies, Studies 103/104. In the placebo group of Studies 103/104, the incidence rates of AST/ALT elevations above threshold (i.e., 3 ×, 5 ×, 8 × ULN) were 5.1%, 1.9%, and 0.5%, respectively (Table 2).

Overall, when comparing the background incidence rates of transaminase elevations above these thresholds among the different age groups, the data showed the incidence was higher in the CF population aged 6 through 11 years.

LUM/IVA versus Placebo Incidence Rates in Subjects Aged 6 Through 11 Years

In subjects aged 6 through 11 years, the incidence rate of elevated transaminases was compared between the LUM/IVA groups of Studies 109 and 011B and the placebo groups of Studies 109 and 770-103 (Table 2).

Overall, the results showed the incidence rate of AST/ALT elevations above threshold that occurred during LUM/IVA treatment was generally **similar** to the background (placebo) incidence rate in this age group.

LFTs are also being assessed in ongoing Study 110. Based on the first 36 weeks of data from Study 011B subjects in Study 110 IA1, the incidence of LFT results that met threshold criteria was lower in Study 110 than during the initial 24 weeks of treatment in Study 011B; the incidence rates of AST/ALT elevations above threshold (i.e., 3 ×, 5 ×, 8 × ULN) were 12.2%, 6.1%, and 4.1%, respectively

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Table 2   Incidence Rate of Transaminase Elevations Above Threshold By Age Group

| | Subjects Aged 6 Through 11 Years | | | | Subjects Aged ≥12 Years | |
| | Study 770-103[a] | Study 011B | Study 109 | | Studies 103/104 | |
Threshold	Placebo N = 26	LUM/IVA N = 58	Placebo N = 101	LUM/IVA N = 103	Placebo N = 370	LUM/IVA N = 738
ALT or AST >3 × ULN	4 (15.4)	11 (19.3)	8 (7.9)	13 (12.6)	19 (5.1)	38 (5.2)
ALT or AST >5 × ULN	1 (3.8)	5 (8.8)	3 (3.0)	5 (4.9)	7 (1.9)	15 (2.0)
ALT or AST >8 × ULN	0	3 (5.3)	2 (2.0)	1 (1.0)	2 (0.5)	6 (0.8)

Sources: VX08-770-103/Table 14.3.4.10.1; VX13-809-011/Table 14.3.4.3.1b; VX14-809-109/Table 14.3.4.3.1; VX12-809-103/104/VX-809 ISS/Table 2.3.3.1

ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVA: ivacaftor; LUM: lumacaftor; ULN: upper limit of normal

[a]   Study 770-103 was a 48-week study, but only data from the first 24 weeks are presented in this analysis for comparison with the 24-week data from Studies 109 and 103/104.

Elevated Transaminases Adverse Events of Special Interest

Background Incidence Rates by Age Group

In the placebo group of Study 109, the overall background incidence rate of elevated transaminase AESIs was 9.9%, while the incidence rate for these same AESIs that led to treatment discontinuation or that were considered serious was 2.0% each (Table 3). Overall, the data suggest the background prevalence of elevated transaminase AESIs, including those leading to treatment discontinuation or considered serious, is relatively common in this younger CF population. In the CF population aged 12 years and older, the background incidence rate of transaminase elevation AESIs was determined based on the placebo data from Studies 103/104. In the placebo group of Studies 103/104, the overall background incidence rate of elevated transaminase AESIs was 4.6% (Table 3). There were no AESIs that led to treatment discontinuation or that were considered serious in this age group.

Overall, when comparing the background incidence rate of elevated transaminase AESIs, including those leading to treatment discontinuation or considered serious, among the different age groups, the results showed the incidence was higher in the younger CF population.

LUM/IVA versus Placebo Incidence Rates in Subjects Aged 6 through 11 Years

In subjects aged 6 through 11 years, the incidence rate of elevated transaminase AESIs between the LUM/IVA groups of Studies 011B and 109 and the placebo group of Study 109 was compared. Overall, the results showed the incidence rates of elevated transaminase AESIs, including those leading to treatment discontinuation or considered serious, were generally similar between both the LUM/IVA and placebo treatment groups in this age group.

Table 3   Incidence Rate of Transaminase Elevations AESIs By Age Group

Event	Subjects Aged 6 Through 11 Years			Subjects Aged ≥12 Years	
	Study 011B	Study 109		Studies 103/104	
	LUM/IVA N = 58	Placebo N = 101	LUM/IVA N = 103	Placebo N = 370	LUM/IVA N = 738
Subjects with any AESI of elevated transaminases	7 (12.1)	10 (9.9)	10 (9.7)	17 (4.6)	38 (5.1)
Subjects with events leading to treatment discontinuation	1 (1.7)	2 (2.0)	2 (1.9)	0	1 (0.1)
Subjects with serious events	1 (1.7)	2 (2.0)	0	0	4 (0.5)

Sources: VX13-809-011/Table 14.3.1.3.3b; VX14-809-109/14.3.1.9.1; VX12-809-103/104/VX-809 ISS/Table 2.2.3.4
AESI: adverse event of special interest; IVA: ivacaftor; LUM: lumacaftor

Other Hepatobiliary Events

In Studies 103/104, conducted in subjects aged 12 years and older, there were 3 subjects with serious AEs involving concurrent elevations in transaminases (ALT or AST) and total bilirubin, which were reported as cholestasis, hepatitis, or hepatitis cholestatic. In Studies 011B and 109, conducted in subjects aged 6 through 11 years, all LFT abnormalities had isolated transaminase elevations without concurrent elevations in total bilirubin.

Ivacaftor Exposure in the LUM/IVA Combination Regimen

The association between IVA and LFT abnormal is yet to be confirmed.

Although the IVA exposure in the LUM/IVA combination dosing regimen for subjects aged 6 through 11 years is higher than that in subjects aged 12 years and older, it is still substantially lower than that of IVA monotherapy. As such, the IVA exposure is not considered as a potential contributing factor for these LFT elevations.

Conclusion

The background incidence rate of transaminase elevations and similar AEs was more common in subjects with CF aged 6 through 11 years than in subjects aged 12 years and older. The higher incidence rate of elevated transaminases observed in Studies 011B and 109 compared to Studies 103/104 is likely attributable to the higher background incidence rate seen in the younger CF population. However, the potential for drug-induced liver injury cannot be excluded. Therefore, the Orkambi SmPC contains warnings for elevated transaminases, including those with concurrent bilirubin elevations, while on LUM/IVA treatment and recommends routine LFT monitoring. Based on review of available clinical data in subjects aged 6 through 11 years, the warnings and recommendations with regard to hepatobiliary events in the current product labelling are considered sufficient.

A submission for a proposed indication extension of Orkambi for the treatment of CF in patients 6 through 11 years of age who are homozygous for F508del included further details summarizing the hepatobiliary data in subjects aged 6 through 11 years from Studies 011B and 109, and a proposed revision to the SmPC (Section 4.8) that includes descriptions of hepatobiliary data for subjects aged 6 through 11 years. In ongoing and future studies involving pediatric subjects, LFTs will be closely monitored.

Assessment of the MAH's response

Despite the data provided suggest higher background incidence rates of transaminase elevations in the CF population aged 6 through 11 years vs. patients aged 12 years or above, the Applicant still has not

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explained why the observed incidence rates of transaminase elevations in Study 011B are higher than those of the active group in Study 109. Further, data shown in Table 2 above does not support the claim on "the incidence rate of AST/ALT elevations above threshold that occurred during LUM/IVA treatment was generally similar to the background (placebo) incidence rate in this age group". Although the potential for drug-induced liver injury in patients 6 through 11 years of age will be acknowledged in the proposed revised SPC of the extension for indication, no specific risk mitigation strategies will be adopted as per request. Therefore, the response above is not considered satisfactory. **The point is not resolved.**

Question 5

Given the SAE of Case was considered to be possibly related to study drug, the Applicant should clarify whether the SAE was an expected adverse event as per Investigator's brochures, or a Suspected Unexpected Serious Adverse Reactions (SUSAR) report had been submitted.

Summary of the MAH's response

The LUM/IVA Investigator's Brochure (IB) is the reference safety information for clinical studies using LUM/IVA (LUM/IVA IB, version 1.0, dated 16 June 2015). Elevations in transaminases, including AST and ALT, are described as ADRs in the IB. Therefore, the event for one Subject was assessed as expected and was not reported as a SUSAR.

Assessment of the MAH's response

Given Study 011B was initiated on 15 January 2015, it would not be possible to apply LUM/IVA IB, version 1.0, dated 16 June 2015, as the Reference Safety Information (RSI). Further, the RSI in IB, i.e., Table 8-1 Incidence of Adverse Drug Reactions, and Section 8.6.1.1 Description of Selected Adverse Drug Reactions of IB does not include such SAE occurred in one Subject. Therefore, as per guidance CT1 section 2.3. (32.), CT3 sections 7.2.3.1. and 7.2.3.2., a SUSAR report should have been submitted. Hence the response is not satisfactory. **The point is not resolved.**

Question 6

The statement, "The overall data acquired to-date does not suggest an association between IVA treatment and cataract development" is contradictory to "a potential association has not been fully excluded" and should be deleted, given an adverse event of cataract considered by the investigator to be possibly related to study drug and the juvenile rat toxicity study demonstrating lens opacities in some animals.

Summary of the MAH's response

Although cases of cataracts have been reported in both programs, the overall findings have not yet indicated a likely causal association with IVA or LUM/IVA treatment. Nearly all cataracts reported in humans have been associated with confounding risk factors, such as steroid use, exposure to radiation, or diabetes. When coupled with the high background prevalence of lens opacities in patients with CF, the overall clinical evidence accumulated to date does not support a direct association between IVA or LUM/IVA and cataracts. Nevertheless, the nonclinical findings of cataracts in newborn rats present a potential association with IVA treatment that cannot be completely excluded in humans at this time.

Assessment of the MAH's response

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The response above is contradictory to itself, as "a potential association between cataracts and IVA treatment still cannot be completely excluded in humans". **<u>The point is not resolved.</u>**

Question 7

The Statistical Analysis Plan Part B states "One unplanned interim analysis (IA) was conducted after all subjects completed Week 4, with a data snapshot date of 19 June 2015." and "The DMC conducted one review of the study safety data, with the same data snapshot date as the one used for the interim analysis." The Applicant should provide the minutes from the IDMC.

Summary of the MAH's response

The unplanned interim analysis was conducted to address a DMC review of Study 011 data and to provide sample size information potentially relevant to Study 109. The DMC recommendation was to allow the study to go forward per protocol without changes. Minutes (dated 14 September 2015) from the DMC review of the interim analysis data and the v1.0 and v2.0 SAPs for IA1, dated 18 June 2015 and 26 August 2015are included with this response.

Assessment of the MAH's response

The Applicant provided the DMC meeting minutes that took place on 14 September 2015, which confirm the DMC recommendations as stated by the Applicant. The point is resolved.

Question 8

The Applicant is requested to present the results for the secondary endpoints as well as the characteristics of the patients before and after the unplanned interim analysis to provide reassurance that the integrity of the trial has not been compromised.

Summary of the MAH's response

Study 011B was an open-label study, thus, the integrity of the trial, including the secondary endpoints, was not compromised by the interim analysis, which was conducted to address a DMC review of Study 011 data. In addition, the data were reviewed internally to provide sample size information potentially relevant to Study 109 (no changes were made to the Study 109 protocol as a result of the review). The interim analysis was conducted after all subjects completed at least the Week 4 Visit of Study 011B. As the interim analysis was conducted after all subjects were enrolled and had completed at least the Week 4 Visit, the characteristics, including demographic and baseline characteristics and PD outcomes, were not meaningfully different from those reported at the corresponding time point in the final clinical study report.

Assessment of the MAH's response

The Applicant states that the interim analysis took place after all subjects had completed at least the Week 4 Visit of Study 011B. Therefore it is agreed that the characteristics of subjects before and after the interim analysis will remain the same. The point is resolved.

Question 9

The Applicant is requested to present analysis for sweat chloride where the worst value is used instead of the median values, when replicate values are available.

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Summary of the MAH's response

There were no subjects with multiple measurements at any time point. Therefore only 1 sweat chloride measurement per subject was used for all analyses.

Assessment of the MAH's response

The Applicant confirms that all subjects had only one sweat chloride measurement. The point is resolved.

Question 10

The Applicant is requested to justify why change from baseline to Day 15 and Week 4 was calculated using the average of Day 15 and Week 4 for sweat chloride.

Summary of the MAH's response

The main statistical analysis for this endpoint was performed on the basis that a similar effect was anticipated for the sweat chloride response at Day 15 and Week 4; the estimated treatment effects were averaged to reduce variability and increase the confidence in the point estimate. Supportive analyses were also conducted to summarize the absolute change from baseline in sweat chloride at each visit, which confirmed the anticipated similar effect at each time point. The within-group LS mean absolute change from baseline in sweat chloride was -20.4 mmol/L (95% CI: -23.9, -16.9; $P<0.0001$) at Day 15 and -19.0 mmol/L (95% CI: -22.9, -15.2; $P<0.0001$) at Week 4.

Assessment of the MAH's response

The Applicant explains that similar effect was anticipated for sweat chloride response at Day 15 and Week 4. It is agreed that taking the average value decreases the uncertainty in the estimate. The point is resolved.

Question 11

There were seven subjects with important protocol violations. The Applicant is requested to assess the impact of these violations on the assessment of secondary endpoints.

Summary of the MAH's response

Based on the intention-to-treat principle, all available data were included in the analyses to provide a conservative approach for data interpretation. The impact of the important protocol deviations (IPDs) on the secondary endpoints is considered minimal to negative.

The following 7 subjects had IPDs during Study 011B (VX13-809-011/Section 10.5.2):

Two subjects had treatment compliance <80%: 1 subject (treatment compliance of 75%) had treatment interrupted for a total of 42 days due to AEs of increased ALT and AST values; 1 subject (treatment compliance of 38.1%) had treatment interrupted for a total of 13 days and was discontinued from treatment due to an AE of urticaria. Given that these subjects had lower exposure to LUM/IVA, including these subjects in the analyses could have reduced the apparent treatment effect observed.

Four subjects did not have an ophthalmologic examination at the Week 24 Visit or the Week 26 Safety Follow-up Visit. These IPDs would not have impacted the assessment of the secondary endpoints,

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which evaluated the PD and PK of LUM/IVA treatment. Two of the 4 subjects rolled over to ongoing Study 110 and had a follow-up ophthalmologic examination in the study.

One subject did not meet an inclusion criterion (inclusion criterion 5: subjects who are homozygous for the *F508del-CFTR* mutation) and was enrolled. This subject was discontinued from treatment and the study (the last dose was Day 18). The limited data included for this subject are unlikely to have impacted the results in a meaningful way.

Assessment of the MAH's response

The exclusion of two subjects for compliance <80% and one subject who did not meet the inclusion criterion 5 from analysis of secondary endpoints is contradictory to the stated intention-to-treat principle, and therefore is not considered as a conservative approach for data interpretation. Further, the study protocol does not explicitly allow such exclusion from analysis. The claim on "the impact of the important protocol deviations (IPDs) on the secondary endpoints is considered minimal to negative" is lacking supportive evidence. **The point is not resolved.**

Conclusion

The response to the request for supplementary information from the MAH is not considered satisfactory, as the safety concerns have not been fully addressed and there seems to be issues of trial conduct.

Safety:

Despite the data provided suggest higher background incidence rates of transaminase elevations in the CF population aged 6 through 11 years vs. patients aged 12 years or above, the Applicant has not explained why the observed incidence rates of transaminase elevations in Study 011B are higher than those of the active group in Study 109. Further, data shown in Table 2 above does not support the claim on "the incidence rate of AST/ALT elevations above threshold that occurred during LUM/IVA treatment was generally similar to the background (placebo) incidence rate in this age group". Although the potential for drug-induced liver injury in patients 6 through 11 years of age will be stated in the proposed revised SPC of the extension for indication, no specific risk mitigation strategies will be adopted. The response regarding a potential association between cataracts and IVA treatment in humans is contradictory to itself.

Trial Conduct:

The MAH claims that the decline in ppFEV1 measurement at Week 8 only could be attributable to an intrinsic variability in FEV1 measurements, rather than a genuine clinically relevant event. However, the MAH has not yet fully investigated this.

Given Study 011B was initiated on 15 January 2015, it would not be possible to apply LUM/IVA IB, version 1.0, dated 16 June 2015, as the Reference Safety Information (RSI). Given an open-label nature without a control group of the study, adhering to the RSI for determining expectedness of AEs is crucial. On the basis of information provided, the SAE of one Case should have been reported as a SUSAR.

The exclusion of two subjects for compliance <80% and one subject who did not meet the inclusion criterion 5 from analysis of secondary endpoints is not in line with the study protocol which does not

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explicitly allow such exclusion. The claim on "the impact of the important protocol deviations (IPDs) on the secondary endpoints is considered minimal to negative" is lacking supportive evidence.

The risk-benefit assessment in subjects aged 6 through 11 years with CF is hence still not determinable. The data of Study 011B should be scrutinised along with results from Study VX14-809-109 (Study 109) and Study VX14-809-110 (Study 110).

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4. Assessment of the second responses to the request for supplementary information

BACKGROUND

Study 011 was submitted to the EMA under Article 46 of Regulation (EC) No 1901/2006 on 15 November 2016. Following Day 60 of the procedure the CHMP assessment report (dated 26 January 2017) included a Request for Supplementary Information. The MAH provided responses to the requested clarifications (dated 17 March 2017).

The Rapporteur's second assessment report (dated 21 April 2017) considered Questions 2, 3, 4, 5, 6, and 11 to remain unresolved, and requested further responses. In a teleconference on 26 May 2017 with the Rapporteur's assessment team, the MAH sought clarification on 3 of the outstanding questions (Questions 3, 5, and 6 [Module 1.2/Annex 5.14 - MHRA Rapporteur Clarification Meeting Minutes]). The MAH acknowledged that some of the previous responses could have been clearer and were not considered to fully address the questions. This document provides further responses to the 6 questions considered unresolved in the Rapporteur's assessment report dated 21 April 2017 (Questions 2, 3, 4, 5, 6, and 11).

Question 2

The Applicant should provide a full explanation on the deterioration in ppFEV1 at Week 8.

Summary of the MAH's response

The MAH acknowledged that the value for ppFEV1 at Week 8 of Study 011B was lower than those at other time points during the Treatment Period. However, it represented -1.2 percentage points below the baseline and was not statistically significant. The variability in FEV1 is a known characteristic in patients with CF, which can lead to inter- and/or intra-individual fluctuations in measurements over time as presented in Figure 1, rather than to variability in the spirometry measurements in the study.

Figure 1   Progressive Lung Disease in a Patient With CF, Homozygous for *F508del*

Source: Vertex Pharmaceuticals' presentation to the FDA Advisory Committee, May 12 2015[5]

Further, among the 31 subjects who had an absolute change in ppFEV1 ≤0 at Week 8, the ppFEV1 values for 15 subjects returned near to or above baseline at the next visit and the ppFEV1 values for the other 16 subjects remained below baseline at the next visit. Only 1 (1.7%) of the 31 subjects discontinued treatment due to adverse events (AEs) (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] increased). The ad-hoc analysis revealed neither any consistent trend across subjects or time points, or any evidence suggesting that AEs of respiratory events, PExs of CF, or upper respiratory infection led to a symptomatic ppFEV1 decline at Week 8.

Given the spirometry methods used in the study were standardized and validated, the lack of evidence for clinically meaningful findings associated with the mean ppFEV1 value at Week 8, and considering that the mean data points for ppFEV1 at all other time points were positive, the MAH did not believe that the mean ppFEV1 measurement at Week 8 would be clinically meaningful.

Assessment of the MAH's response

Given above explanation, it can be agreed that the observed lower values of ppFEV1 at Week 8 could be inter- and intra-individual fluctuations in measurements over time, rather than having any statistical or clinical significance. The MAH also clarified that the spirometry methods used in the study were standardized and validated. The point is considered resolved.

Question 3

The study report stating, in Part B, the most common AEs (≥15%) by PT were cough (29 [50.0%] subjects), nasal congestion (12 [20.7%] subjects), infective pulmonary exacerbation of CF (12 [20.7%] subjects), and headache (12 [20.7%] subjects). These AEs were mostly expected manifestations of CF disease." should be clarified, i.e., whether they are related to the IMP or not. As per guidance CT1 section 2.3. (32.), CT3 sections 7.2.3.1. and 7.2.3.2., AEs should be categorised as expected vs. unexpected to the IMP by the nature or severity of which not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)' and an increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Summary of the MAH's response

The MAH acknowledged that use of the word "expected" in this response was unclear in the context of the requirements of CT-3 and confirmed that the expectedness was assessed according to the RSI in the Investigator's Brochure (IB) during Study 011B as per EU Clinical Trial Guidance.

Assessment of the MAH's response

The MAH has clarified that the trial safety assessment for Study 011B was in line with the EU CT guidance. The point is resolved.

Question 4

The Applicant is required to address the following comments based on the data provided:

Although LUM 100 mg/IVA 125-mg FDC tablet q12h seems to be well tolerated in subjects aged 6 through 11 years with CF, there are serious safety concerns, especially on the hepatic events:

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- Given Part B designed to capture adverse reactions, i.e., a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%, the observed 7 (12.1%) subjects with elevated transaminases (AST or ALT >5x ULN) suggest a significant incidence of hepatic injury.

- The rates of observed AST or ALT >3x ULN or above are much higher than those described in the SPC, i.e., clinical studies with 24 weeks of treatment with lumacaftor/ivacaftor in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The study report also states "Although the incidences of transaminases elevations (ALT or AST) appeared to be higher than that observed in subjects aged 12 years and older (Studies VX12-809-103 and VX12-809-104), these are generally consistent with observations in subjects of the same age group from previously completed placebo-controlled IVA monotherapy studies and the information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults."

Given that ivacaftor steady state levels appear to be higher in the Part B study compared to the pooled data from study 103 and 104, the observed higher incidence of transaminases elevations seems to be relevant to IVA. Further, according literature, persistent elevations of AST, ALT or GGT more than 3 times the upper limit of normal in children aged >2 years with CF were very rare. Therefore, the statement "transaminase elevations are more common in younger patients with CF than in adults" for rationalizing the observed elevated AST/ALT cannot be agreed.

- One Case had re-elevation of AST/ALT after resumption of LUM/IVA and hence the treatment was withdrawn. The causal relationship suggests a drug-induced liver injury.

And the Applicant is required to provide the following information:

1) Comparing above liver events with similar events in adults and adolescents [including any safety paediatric reports received by the company and any included in the Periodic Safety Update Reports (PSURs)].

2) Comparing above liver events with those in pivotal studies, i.e., Study VX14-809-109 and Study VX15-809-110 from minutes of IDMC and Development Safety Update Reports (DSURs).

3) Implications for the SmPC, PIL, and future paediatric studies, and proposal for amendments with justification.

Summary of the MAH's response

The MAH discussed the differences in transaminase elevations between Study 011B and Study 109 and between lumacaftor/ivacaftor (LUM/IVA) and placebo treatments.

LUM/IVA Treatment: Study 011B Versus Study 109 LUM/IVA Group

Overall, there were no meaningful differences in the subject profiles between studies that would explain the difference in incidence of treatment-emergent transaminase elevations in LUM/IVA-treated subjects. Following a LUM 200 mg/IVA 250 mg every 12 hours (q12h) regimen for 24 weeks, the concentrations of LUM and IVA were similar in Study 011B and Study 109. Given the relatively small numbers of subjects with transaminase elevations in both studies, the difference in transaminase elevations was considered likely to be due to inter-study variability in this population who had high background liver function abnormalities associated with CF liver disease.

LUM/IVA and Placebo Treatment: Study 011B and Study 109 LUM/IVA Group Versus Study 109 Placebo Group

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The MAH acknowledged that the percentage of subjects with transaminase elevations was numerically higher in LUM/IVA-treated subjects in Study 011B and Study 109 relative to the placebo group in Study 109. Transaminase elevations across both Study 011B and Study 109 were isolated lab abnormalities (i.e., without concurrent bilirubin elevation) and most subjects remained on treatment or resumed treatment after interruption without further elevations. As summarized in Table 3, the percentage of subjects who had discontinuations due to AEs of special interest (AESIs) of elevated transaminases was low and comparable between the LUM/IVA-treated subjects and the placebo group Study 109 (3 of 161 LUM/IVA-treated subjects in Study 011B and Study 109, and 2 of 101 placebo subjects in Study 109). In addition, the percentage of subjects with AESIs of elevated transaminases was comparable between the LUM/IVA-treated subjects and the placebo group Study 109 (17 of 161 LUM/IVA-treated subjects in Study 011B and Study 109, and 10 of 101 placebo subjects in Study 109).

Table 3   Summary of Elevated Transaminase AESIs by Preferred Term

AESI Preferred Term	Study 011B LUM/IVA N = 58	Study 109 Placebo N = 101	Study 109 LUM/IVA N = 103
Subjects with any AESI of elevated transaminases	7 (12.1)	10 (9.9)	10 (9.7)
ALT increased	7 (12.1)	9 (8.9)	8 (7.8)
AST increased	4 (6.9)	7 (6.9)	6 (5.8)
Transaminases increased	0	1 (1.0)	2 (1.9)
Subjects with events leading to treatment discontinuation	1 (1.7)	2 (2.0)	2 (1.9)
Subjects with events leading to treatment interruption	3 (5.2)	0	3 (2.9)
Subjects with serious events	1 (1.7)	2 (2.0)	0
Subjects with related serious events[a]	1 (1.7)	2 (2.0)	0

Sources: VX13-809-011/Table 14.3.1.3.3b and VX14-809-109/Table 14.3.1.9.1
AESI: adverse event of special interest; ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVA: ivacaftor; LUM: lumacaftor; N: total sample size of the Safety Set; q12h: every 12 hours
Notes: A subject with multiple events within a category is counted only once in that category.
[a]   Related serious AEs include related, possibly related, and missing categories.

In the proposed SmPC submitted in the Line Extension on March 03 2017 and currently under review (EMEA/H/C/003954/X/0020), the monitoring recommendations were proposed to be unchanged but a description of the transaminase elevations in Study 011B and Study 109 was added, to ensure that appropriate information will be available for prescribers, caregivers, and patients.

In conclusion, the MAH considers that the current warnings and precautions, including monitoring recommendations, are appropriate and sufficient to monitor and manage transaminase elevations in patients of this age group. The MAH will continue to monitor transaminase elevations as part of post-marketing pharmacovigilance surveillance, and evaluate the need for additional risk management or other actions, as appropriate.

Assessment of the MAH's response

The MAH explained that the small number of subjects with transaminase elevations in both studies was likely to be due to inter-study variability in this population who had high background liver function abnormalities associated with CF liver disease and would like to continue monitoring transaminase elevations as part of post-marketing pharmacovigilance surveillance and evaluating the need for additional risk management or other actions, as appropriate. The relevant sections in the SmPC are under review (EMEA/H/C/003954/X/0020). This can be accepted. The point is resolved.

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Question 5

Given the SAE of one Case was considered to be possibly related to study drug, the Applicant should clarify whether the SAE was an expected adverse event as per Investigator's brochures, or a Suspected Unexpected Serious Adverse Reactions (SUSAR) report had been submitted.

Summary of the MAH's response

The MAH clarified that the case was in fact assessed against the RSI in place at the time (LUM IB, version 7.0 [dated 27 March 2014]) as unexpected and expedited as a SUSAR (case number: XXXX) on 06 May 2015 with follow-up reports on 14 May 2015, 28 May 2015, and 22 June 2015. In the response dated 17 March 2017, the MAH stated "the event for one Subject was assessed as expected" in error.

Assessment of the MAH's response

The MAH has confirmed that the queried case had been submitted as a SUSAR. This is acceptable. The point is resolved.

Question 6

The statement, "The overall data acquired to-date does not suggest an association between IVA treatment and cataract development" is contradictory to "a potential association has not been fully excluded" and should be deleted, given an adverse event of cataract considered by the investigator to be possibly related to study drug and the juvenile rat toxicity study demonstrating lens opacities in some animals.

Summary of the MAH's response

The MAH clarified that the statement "The overall data acquired to-date does not suggest an association between IVA treatment and cataract development" was not intended as to refute the potential association between cataracts and IVA treatment. Although risk factors were present in some cases, a possible risk attributable to IVA cannot be excluded.

Assessment of the MAH's response

Given above clarification, the MAH did not intend to refute the potential association between cataracts and IVA treatment, the point is considered resolved.

Question 11

There were seven subjects with important protocol violations. The Applicant is requested to assess the impact of these violations on the assessment of secondary endpoints.

Summary of the MAH's response

Consistent with the intention-to-treat principle, all subjects (including the 7 with important protocol deviations (IPDs)) were included in the analyses as defined by the Study 011 protocol and statistical analysis plan. Therefore, all available data for the 2 subjects with compliance <80% and the subject who did not meet inclusion criterion 5 were included in the analysis. None of the subjects with IPDs were excluded from the analysis.

Assessment of the MAH's response

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The MAH has confirmed that none of the subjects with IPDs were excluded from the analysis. This is acceptable. The point is resolved.

CONCLUSIONS

The MAH has addressed all questions raised during the procedure satisfactorily. There are no further points. The benefit-risk assessment is considered favourable.

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