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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/P46/017

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	25 April 2022	25 April 2022	☐
☐	CHMP Rapporteur Assessment Report	30 May 2022	30 May 2022	☐
☐	CHMP members comments	13 June 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16 June 2022	n/a	☐
☒	CHMP adoption of conclusions:	23 June 2022	23 June 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On 25/04/2022, the MAH submitted a completed paediatric study for Orkambi, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The Study VX16-809-121(abbreviated as Study 121) is a stand-alone study post- authorization measure (PAM) under Article 46 of Regulation (EC) No 1901/2006.

2.2. Information on the pharmaceutical formulation used in the study

The following formulations and compositions have been used in the study:

- LUM 100 mg/IVA 125 mg fixed-dose combination (FDC) granules (stick pack)
- LUM 150 mg/IVA 188 mg FDC granules (stick pack)
- LUM 0 mg/IVA 0 mg matching placebo granules (stick pack)
- LUM 100 mg/IVA 125 mg IVA FDC tablets

2.3. Clinical aspects

2.3.1. Introduction

CF is an autosomal recessive genetic disease with serious, chronically debilitating morbidities and high premature mortality. Lumacaftor/ivacaftor (LUM/IVA; VX-809/VX-770; Orkambi™) is a medicine designed to treat the underlying molecular defect and enhance the function of CFTR in patients homozygous for the F508del-CFTR mutation (F/F) as young as 2 years of age.

CF greatly affects the paediatric population, as nearly half of the total CF population is less than 18 years of age. Even before the widespread adoption of newborn screening, the majority of patients with CF were diagnosed in infancy or early childhood due to manifestations of the disease. Pancreatic destruction leading to pancreatic exocrine insufficiency begins in utero, and lung involvement is manifest by pulmonary inflammation and infection that begins shortly after birth.

The MAH submitted a final report for Study 121.

Clinical study number and title

Description

Study 121, an exploratory Phase 2, randomized, double-blind, placebo-controlled, multicentre study designed to explore the impact of LUM/IVA on disease progression in subjects aged 2 through 5 years with Cystic fibrosis (CF), homozygous for F508del.

The present study was designed to explore the long-term disease progression and efficacy of LUM/IVA in subjects 2 through 5 years of age, homozygous for F508del in a placebo-controlled setting, with a window of opportunity to halt disease progression and prevent organ damage by early intervention

with therapies that treat the underlying cause of CF. The impact of LUM/IVA on lung function was explored using 2 methods:

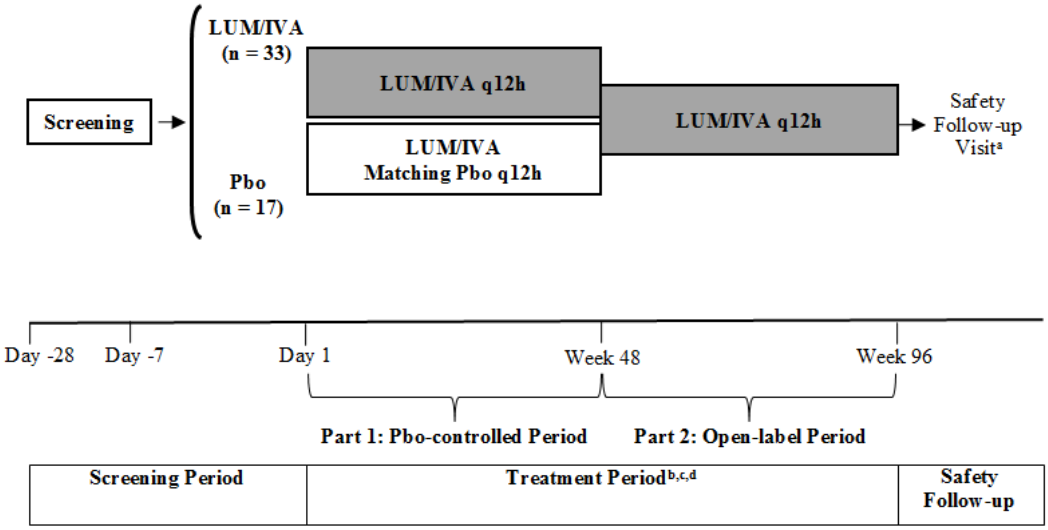
1) thoracic magnetic resonance imaging (MRI), an imaging assessment used to determine structural and functional lung abnormalities and to monitor disease progression and

2) LCI, a measure of ventilation inhomogeneity that is based on tidal breathing techniques that have been evaluated in patients as young as infants.

The long-term data are aimed to provide information about disease progression and the potential for disease modification by early CFTR-targeted intervention and to support the efficacy and safety of LUM/IVA in this younger CF population.

Methods

Figure 1: Schematic of Study Design



ETT: Early Termination of Treatment; LUM/IVA: lumacaftor/ivacaftor; Pbo: placebo; q12h: every 12 hours
a The Safety Follow-up Visit was scheduled to occur 2 weeks (± 4 days) after the last dose, as described in Appendix 16.1.1/Protocol Version 4.0/Section 9.1.3.
b In Part 1, approximately 50 subjects were planned to be randomized (2:1) to receive LUM/IVA or placebo.
Subjects received LUM 100 mg/IVA 125 mg q12h (subjects weighing <14 kg at screening), LUM 150 mg/IVA 188 mg q12h (subjects weighing ≥14 kg at screening), or matching placebo, regardless of age. In Part 2, subjects <6 years of age and weighing <14 kg received LUM 100 mg/IVA 125 mg q12h; subjects <6 years of age and weighing ≥14 kg received LUM 150 mg/IVA 188 mg q12h; and subjects ≥6 years of age received LUM 200 mg/IVA 250 mg q12h.
c No downward dose adjustments were made if a subject's weight decreased. Doses may have been adjusted upward for changes in weight and age, as described in Appendix 16.1.1/Protocol Version 4.0/Section 9.6.

d Subjects who prematurely discontinued study drug had an ETT Visit as soon as possible.

Study participants

Table 2 Key Eligibility Criteria in Study 121

Inclusion Criteria	Exclusion Criteria
• Confirmed diagnosis of CF as determined by sweat chloride ≥60 mmol/L and clinical manifestations of CF • F/F *CFTR* genotype • 2 through 5 years of age (inclusive) weighing ≥8 kg	• History of any illness or clinical condition that could confound the results of the study • Any protocol-defined laboratory values indicative of abnormal hemoglobin, liver function, or abnormal renal function, or other clinically significant laboratory abnormalities at Screening • An acute upper or lower respiratory infection, pulmonary exacerbation(s), or changes in therapy for pulmonary disease within 28 days before first dose of study drug • An acute illness not related to CF within 2 weeks before first dose of study drug • History of solid organ or hematological transplantation • Inability of the subject to perform MBW assessment during Screening • History of cataract/lens opacity or evidence of clinically significant cataract/lens opacity determined to be clinically significant during Screening

Sources: Study 121 CSR/Section 9.3.1 and Section 9.3.2
CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; CSR: clinical study report; F/F: homozygous for *F508del*; MBW: multiple-breath washout

Treatments

Dose of LUM/IVA

Subjects were randomized 2:1 to receive LUM/IVA or placebo. The dose regimens of LUM 100 mg/IVA 125 mg every 12 hours (q12h; subjects weighing <14 kg at screening) and LUM 150 mg/IVA 188 mg q12h (subjects weighing ≥14 kg at screening) were chosen based on Study 115A, a safety and PK study of LUM/IVA in subjects 2 through 5 years of age, and an interim analysis of confirmatory PK data obtained during Study 115B. Subjects who turned 6 years of age at or after the Week 48 Visit received LUM 200 mg/IVA 250 mg q12h (starting at the Week 48 Visit or the next scheduled visit after turning 6 years of age), regardless of weight.

Duration of Dosing

The duration of 48 weeks of placebo-controlled treatment in Part 1, plus an additional 48 weeks of open-label LUM/IVA treatment in Part 2, was expected to provide an adequate assessment of efficacy and safety, including long-term impact on disease progression, in particular, structural damage assessed via MRI. If the Treatment Period was extended to allow for recovery from a pulmonary exacerbation (PEx) and the Week 48 and/or Week 96 Visit was delayed, subjects continued to take study drug until the Week 48 and/or Week 96 Visit was completed.

Objective(s)

Primary objective: to explore the impact of LUM/IVA on disease progression in subjects aged 2 through 5 years with CF, homozygous for *F508del*.

Secondary objective: to explore the relationship between lung clearance index (LCI) and imaging modalities for LUM/IVA in subjects aged 2 through 5 years with CF, homozygous for *F508del*.

Outcomes/endpoints

The **primary endpoint** was the absolute change from baseline in magnetic resonance imaging (MRI) global chest score at Week 48. Secondary endpoints included the absolute change from baseline in

number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value (LCI2.5) through Week 48 and growth parameters at Week 48.

Sample size

The proposed sample size of 50 subjects (2:1 randomization: 33 LUM/IVA subjects and 17 placebo subjects) is based on the number of potential subjects expected to be available for participation. No formal sample size calculation was conducted.

Randomisation

Study Part 1

The proposed sample size of 50 subjects will be randomized by 2:1 ratio to the LUM/IVA arm or placebo arm. An interactive web or voice response system (IXRS) will be used to assign subjects to treatment or placebo. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor.

Study Part 2

Part 2 is an open-label extension period. Randomization is not applicable.

Blinding (masking)

Subjects/caregivers and all site personnel, including the investigator, the study monitor, and the study team, were blinded until database lock for Part 1 (i.e., database lock for data up to and including the Week 48 Visit). Unblinding of an individual subject's treatment by the investigator was limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study drug was necessary for clinical management.

Statistical Methods

Unless otherwise specified, all efficacy analyses described in this section were based on the FAS and presented by treatment group in Part 1 analysis and by treatment sequence from Part 1 to Part 2 in final analysis. The study baseline was used to calculate the change from baseline for continuous efficacy endpoints.

Primary endpoint

Definition of Endpoint The primary efficacy endpoint was the absolute change from baseline in MRI global chest score at Week 48. MRI Chest Scores: MRI scans were assessed semi-quantitatively via a standardized chest MRI scoring system. Each subject had 6 lobes scored with the lingula treated as a separate lobe. The scoring parameters, score aggregation, and global score calculations are described below. After scans were reviewed, MRI scores were captured using the following 7 scoring parameters for each of the 6 lobes: 1. Bronchiectasis/wall thickening 2. Mucus plugging 3. Abscesses/sacculations 4. Consolidations 5. Special findings 6. Mosaic pattern 7. Perfusion abnormalities.

Primary Analysis The primary analysis was performed using Bayesian methods. Specifically, the actual Bayesian posterior probability of LUM/IVA being superior to placebo in the MRI global chest score at Week 48 was calculated using a vague normal prior distribution. In addition, descriptive summary statistics for both between-treatment group difference and within-treatment group change at Week 48 were presented. Descriptive summary statistics (n, mean, median, SD, minimum, and maximum) with the corresponding 95% CIs were provided

Results

Participant flow and number analysed

In Part 1, 51 subjects were randomized (2:1) to receive LUM/IVA or placebo and received at least 1 dose of study drug. Two subjects in the LUM/IVA group prematurely discontinued from both LUM/IVA treatment and the study. One subject discontinued due to pre-treatment AEs that started 4 days before the first dose of study drug; the subject discontinued after 26 days of LUM/IVA treatment. One subject discontinued for "other" reasons (the subject began taking commercial drug). All other subjects completed treatment and completed the Part 1 study. Forty-nine subjects continued to Part 2.

Table 10-1 Subject Disposition (All Subjects Set)

	n (%)[a]		
Disposition/Reason	PBO N = 16	LUM/IVA N = 35	Total N = 51
All Subjects Set[b]	16	35	51
Safety Set[c]	16	35	51
Randomized but never dosed	0	0	0
Full Analysis Set	16	35	51
Completed treatment	16 (100.0)	33 (94.3)	49 (96.1)
Prematurely discontinued treatment	0	2 (5.7)	2 (3.9)
Reason for treatment discontinuation			
AE	0	1 (2.9)[d]	1 (2.0)
Other	0	1 (2.9)	1 (2.0)
Completed study	16 (100.0)	33 (94.3)	49 (96.1)
Prematurely discontinued study	0	2 (5.7)	2 (3.9)

Table 10-1 Subject Disposition (All Subjects Set)

	n (%)[a]		
Disposition/Reason	PBO N = 16	LUM/IVA N = 35	Total N = 51
Reason for study discontinuation			
AE	0	1 (2.9)[d]	1 (2.0)[d]
Withdrawal of consent (not due to AE)	0	1 (2.9)	1 (2.0)
Continued to Part 2	16 (100.0)	33 (94.3)	49 (96.1)

Source: Table 14.1.1p

AE: adverse event; FAS: Full Analysis Set; IVA: ivacaftor; LUM: lumacaftor; n: size of subsample; N: total sample size; PBO: placebo; TEAE: treatment-emergent adverse events

[a] Percentages were calculated relative to the number of subjects in the FAS.

[b] The All Subjects Set included all subjects who were randomized or received at least 1 dose of study drug.

[c] The Safety Set included all subjects who received at least 1 dose of study drug.

[d] This AE began pretreatment (Listing 16.2.7.1p) and is therefore not included in Table 12-1 (Overview of AEs) or Table 14.3.2.3.1p (Listing of TEAEs Leading to Treatment Discontinuation). This subject received 26 days of LUM/IVA before discontinuing (Listing 16.2.5.1.1p).

Of the 49 subjects who continued to Part 2 and received at least 1 dose of LUM/IVA in Part 2, 47 (95.9%) subjects completed treatment and 48 (98%) subjects completed the study.

Subject disposition for Part 2 is summarized in Table 10-2. In Part 2, 49 subjects received at least 1 dose of LUM/IVA. Two (4.1%) subjects discontinued LUM/IVA treatment (both due to AEs) and 1 (2.0%) subject discontinued the study. All other subjects completed treatment and completed Part 2.

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

Disposition/Reason	n (%)[a] PBO-LUM/IVA N = 16	LUM/IVA-LUM/IVA N = 33	Total N = 49
Full Analysis Set, Part 2[b]	16	33	49
Safety Set, Part 2[c]	16	33	49
Completed Part 2 treatment	16 (100.0)	31 (93.9)	47 (95.9)
Prematurely discontinued Part 2 treatment	0	2 (6.1)	2 (4.1)
Reason for treatment discontinuation			
AE	0	2 (6.1)	2 (4.1)
Completed study	16 (100.0)	32 (97.0)	48 (98.0)
Prematurely discontinued study during Part 2	0	1 (3.0)	1 (2.0)
Reason for study discontinuation			
AE	0	0	0
Withdrawal of consent (not due to AE)	0	1 (3.0)	1 (2.0)

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

Disposition/Reason	n (%)[a] PBO-LUM/IVA N = 16	LUM/IVA-LUM/IVA N = 33	Total N = 49

Source: Table 14.1.1f

AE: adverse event; FAS: Full Analysis Set; LUM/IVA: lumacaftor/ivacaftor; n: size of subsample; N: total sample size; PBO: placebo

Note: The All Subjects Set, Part 2, included all subjects who participated in study Part 2.

[a] Percentages were calculated relative to the number of subjects in the FAS, Part 2.

[b] Full Analysis Set, Part 2 was defined as all randomized subjects who carried the intended CFTR allele mutation and received at least one dose of study drug during the study Part 1 and received at least one dose of study drug during the study Part 2.

[c] Safety Set, Part 2 was defined as all subjects who received at least 1 dose of study drug in the Part 2.

Recruitment and Baseline data

In Part 1, all 51 subjects were White. The majority of subjects (64.7%) were male, and the mean age at baseline was 4.2 years. The mean body mass index (BMI) was 15.52 kg/m2 and the mean weight was 17.2 kg at baseline. The mean BMI-for-age z-score was -0.16, and the mean weight-for-age z-score was 0.05.

Efficacy results

Primary Endpoint

The primary endpoint was change from baseline in MRI global chest score at Week 48. The probability of LUM/IVA being superior to placebo was 76.23% based on Bayesian posterior probability. The mean (95% CI) difference between LUM/IVA and placebo was -1.5 (-5.5, 2.6) (see table 11-1).

Table 11-1 Summary of MRI Global Chest Score, Change From Baseline, and Bayesian Posterior at Week 48 (Full Analysis Set)

Visit Statistics	PBO N = 16	LUM/IVA N = 35
Study baseline		
n	15	34
Mean (SD)	21.4 (9.3)	17.6 (9.7)
Median	23.0	14.5
Min, max	5, 38	3, 45
Part 1 - Week 48		
n	15	32
Mean (SD)	21.1 (11.1)	16.0 (9.4)
Median	19.0	13.0
Min, max	5, 48	4, 42
Part 1 - absolute change at Week 48		
n	15	32
Mean (SD)	-0.3 (6.1)	-1.7 (6.6)
Median	0.0	-2.5
Min, max	-11, 10	-15, 14
95% CI of mean	(-3.7, 3.1)	(-4.1, 0.7)
Mean difference versus PBO (95% CI)	NA	-1.5 (-5.5, 2.6)
Bayesian posterior probability for treatment difference <0	NA	0.7623

Sources: Table 14.2.1.1p and Table 14.2.1.2p

IVA: ivacaftor; LUM: lumacaftor; MRI: magnetic resonance imaging; max: maximum; min: minimum; n: size of subsample; N: total sample size; NA: not applicable; PBO: placebo

Notes: Study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. Mean difference versus PBO: mean difference (LUM/IVA versus PBO) of absolute change at Week 48. Treatment difference (LUM/IVA versus PBO): posterior mean difference (LUM/IVA versus PBO) of absolute change at Week 48.

Secondary Endpoints

The secondary endpoints were absolute change from baseline in LCI2.5 through Week 48 and the absolute changes from baseline in weight-, stature-, and BMI-for-age z-score at Week 48.

1. Absolute Change in LCI2.5 From Baseline at Week 48

A within-group numerical improvement (i.e., a reduction) in LCI2.5 was observed after treatment with LUM/IVA with a mean (95% CI) absolute change from baseline of -0.37 (-0.85, 0.10) through Week 48 (Table 11-2). A mean absolute increase in LCI2.5 from baseline of 0.32 was observed in the placebo group.

Table 11-2 Summary of $LCI_{2.5}$ Change From Baseline Through Week 48 (Full Analysis Set)

Visit Statistics	PBO N = 16	LUM/IVA N = 35
Study baseline		
n	16	35
Mean (SD)	8.97 (2.42)	8.86 (2.01)
Median	8.01	8.04
Min, max	6.75, 14.10	6.35, 15.71
Part 1 – average through Week 48		
n	16	35
Mean (SD)	9.29 (2.24)	8.49 (1.50)
Median	8.25	8.12
Min, max	6.29, 14.47	6.29, 14.53
Part 1 - absolute change through Week 48		
n	16	35
Mean (SD)	0.32 (0.98)	-0.37 (1.38)
Median	0.42	-0.06
Min, max	-1.21, 2.29	-4.93, 1.70
95% CI of mean	(-0.20, 0.84)	(-0.85, 0.10)

Source: Table 14.2.2.1p

IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to $1/40^{th}$ of its starting value; LUM: lumacaftor; max: maximum; min: minimum; n: size of subsample; N: total sample size; PBO: placebo

Notes: Study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. 95% CIs are provided for the absolute change from baseline based on normal approximation. Average through Week 48 was defined as the average of Weeks 12, 24, 36, and 48.

2. Absolute Change in Weight-for-age Z-score at Week 48

A within-group numerical improvement in weight-for-age z-score was observed after treatment with LUM/IV, with a mean (95% CI) absolute change from baseline of 0.13 (-0.01, 0.27) at Week 48 (Table 11-3). A slight decrease from baseline was observed in the placebo group, with a mean (95% CI) absolute change from baseline of -0.07 (-0.24, 0.11).

Table 11-3 Summary of Weight-for-Age z-score Change From Baseline at Week 48 (Full Analysis Set)

Visit Statistics	PBO N = 16	LUM/IVA N = 35
Study Baseline		
n	16	35
Mean (SD)	0.02 (1.19)	0.06 (0.92)
Median	-0.03	0.08
Min, max	-1.66, 2.49	-1.95, 1.64
Part 1 – Week 48		
n	16	32
Mean (SD)	-0.04 (1.05)	0.19 (0.91)
Median	-0.28	0.21
Min, max	-1.67, 2.23	-2.19, 1.68
Part 1 - absolute change at Week 48		
n	16	32
Mean (SD)	-0.07 (0.33)	0.13 (0.39)
Median	-0.20	0.15
Min, max	-0.43, 0.76	-0.57, 1.16
95% CI of mean	(-0.24, 0.11)	(-0.01, 0.27)

Source: Table 14.2.3.1p

IVA: ivacaftor; LUM: lumacaftor; max: maximum; min: minimum; n: size of subsample; N: total sample size; PBO: placebo

Note: Study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug.

3. Absolute Change in Stature-for-age Z-score at Week 48

A within-group numerical improvement in stature-for-age z-score was observed after treatment with LUM/IVA, with a mean (95% CI) absolute change from baseline of 0.09 (-0.05, 0.22) at Week 48 (Table 11-4). A similar numerical improvement in stature-for-age z-score was observed in the placebo group (0.10).

Table 11-4 Summary of Stature-for-Age z-score Change From Baseline at Week 48 (Full Analysis Set)

Visit Statistics	PBO N = 16	LUM/IVA N = 35
Study baseline		
n	16	35
Mean (SD)	0.08 (1.24)	0.36 (1.06)
Median	-0.09	0.11
Min, max	-1.79, 1.90	-1.66, 2.95
Part 1 – Week 48		
n	16	32
Mean (SD)	0.18 (1.25)	0.40 (1.07)
Median	0.11	0.27
Min, max	-1.86, 2.08	-1.51, 3.19
Part 1 - absolute change at Week 48		
n	16	32
Mean (SD)	0.10 (0.27)	0.09 (0.36)
Median	0.08	0.16
Min, max	-0.41, 0.53	-0.86, 0.83
95% CI of mean	(-0.04, 0.24)	(-0.05, 0.22)

Source: Table 14.2.4.1p
IVA: ivacaftor; LUM: lumacaftor; max: maximum; min: minimum; n: size of subsample; N: total sample size; PBO: placebo
Note: Study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug.

4. Absolute Change Body Mass Index-for-Age Z-score at Week 48

A within-group numerical improvement in BMI-for-age z-score was observed after treatment with LUM/IVA, with a mean (95% CI) absolute change from baseline of 0.20 (-0.02, 0.41) at Week 48. A decrease from baseline was observed in the placebo group, with a mean (95% CI) absolute change from baseline of -0.24 (-0.55, 0.07) (Table 11-5).

Table 11-5 Summary of BMI-for-Age Z-score Change From Baseline at Week 48 (Full Analysis Set)

Visit Statistics	PBO N = 16	LUM/IVA N = 35
Study baseline		
n	16	35
Mean (SD)	0.06 (1.03)	-0.25 (1.14)
Median	-0.05	-0.15
Min, max	-1.64, 2.39	-3.68, 1.70
Part 1 – Week 48		
n	16	32
Mean (SD)	-0.18 (1.20)	0.01 (0.90)
Median	0.04	0.16
Min, max	-3.04, 2.07	-2.21, 1.56
Part 1 - absolute change at Week 48		
n	16	32
Mean (SD)	-0.24 (0.58)	0.20 (0.61)
Median	-0.26	0.14
Min, max	-1.40, 0.95	-1.37, 1.70
95% CI of mean	(-0.55, 0.07)	(-0.02, 0.41)

Source: Table 14.2.5.1p

BMI: body mass index; IVA: ivacaftor; LUM: lumacaftor; max: maximum; min: minimum; n: size of subsample; N: total sample size; PBO: placebo

Notes: Study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part 1. Through Week 48 was defined as the average of the applicable visits up to Week 48.

Additional Endpoints

Additional efficacy endpoints, such as MRI outcomes (i.e., reduction in scores), LCI5.0, additional growth parameters, and markers related to pancreatic function and intestinal inflammation, have been analysed both in a part 1 or final (part 1 and 2) analyses.

Within-group numerical improvements in several efficacy outcomes were observed after 48 weeks of LUM/IVA treatment (see table 11-6)

Table 11-6 Part 1 Analysis: Summary of Additional Continuous Endpoint Results (Full Analysis Set)

Additional Endpoint	PBO N = 16	LUM/IVA N = 35
Absolute change from baseline	**Mean (95% CI)**	**Mean (95% CI)**
MRI		
MRI morphological chest score at Week 48	-0.9 (-3.5, 1.7)	-1.1 (-2.7, 0.6)
MRI perfusion chest score at Week 48	0.5 (-0.9, 1.9)	-0.7 (-1.6, 0.3)
Sweat Chloride and LCI		
Sweat chloride (mmol/L) through Week 48	1.0 (-4.5, 6.6)	-25.4 (-32.0, -18.8)
$LCI_{5.0}$ through Week 48	0.07 (-0.20, 0.33)	-0.20 (-0.41, 0.02)
Growth Parameters		
Weight (kg) at Week 48	1.9 (1.6, 2.1)	2.4 (2.1, 2.8)
Stature (cm) at Week 48	6.9 (6.1, 7.6)	6.9 (6.3, 7.6)
BMI (kg/m^2) at Week 48	-0.36 (-0.68, -0.03)	0.07 (-0.17, 0.30)
Markers of Pancreatic Function and Intestinal Inflammation		
IRT (µg/L) through Week 48	-37.9 (-75.5, -0.2)	-85.5 (-177.9, 6.8)
FE-1 (mg/kg) through Week 48	2.6 (-3.0, 8.2)	37.1 (7.2, 67.0)
Fecal calprotectin (mg/kg) through Week 48	26.14 (-139.85, 192.12)	-133.90 (-231.94, -35.86)

Sources: Tables 14.2.6.1p, 14.2.7.1p, 14.2.8.1p, 14.2.9.1p, 14.2.10.1p, Ad hoc 14.2.12.1p, 14.2.14.1p, 14.2.15.1p, 14.2.16.1p, and 14.2.17.1p

BMI: body mass index; FE-1: fecal elastase-1; IRT: immunoreactive trypsinogen; IVA: ivacaftor; LCI: lung clearance index; $LCI_{5.0}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value; LUM: lumacaftor; MRI: magnetic resonance imaging; N: total sample size; PBO: placebo

Note: Study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. Through Week 48 was defined as the average of all post-baseline measures at scheduled visits up to Week 48.

The final analysis for the additional efficacy endpoints that were continuous are summarized in Table 11-9. Subjects who received LUM/IVA in both Parts 1 and 2 are hereafter referred to as the LUM/IVA-LUM/IVA group. Subjects who received placebo in Part 1 and LUM/IVA in Part 2 are hereafter referred to as the PBO-LUM/IVA group. Because "through Week 96" was defined as the average of all post-baseline measures at scheduled visits up to Week 96, the continuous endpoints from baseline through Week 96 were only applicable to the LUM/IVA-LUM/IVA group.

Table 11-9 Final Analysis: Summary of Continuous Endpoint Results (Full Analysis Set)

Additional Endpoint	PBO-LUM/IVA N = 16	LUM/IVA-LUM/IVA N = 33
Absolute change from baseline	Mean (95% CI)	Mean (95% CI)
MRI		
MRI global chest score at Week 96	-5.6 (-9.2, -1.9)	-2.7 (-5.2, -0.1)
MRI morphological chest score at Week 96	-4.8 (-7.4, -2.1)	-1.9 (-3.8, 0.1)
MRI perfusion chest score at Week 96	-0.8 (-2.3, 0.6)	-0.8 (-1.7, 0.0)
Sweat Chloride and LCI		
Sweat chloride (mmol/L) through Week 96	NA	-26.3 (-33.1, -19.4)
$LCI_{2.5}$ through Week 96	NA	-0.58 (-1.02, -0.14)
$LCI_{5.0}$ through Week 96	NA	-0.25 (-0.46, -0.04)
Growth Parameters		
Weight-for-age z-score at Week 96	0.03 (-0.24, 0.29)	0.09 (-0.03,0.22)
Stature-for-age z-score at Week 96	0.15 (-0.07, 0.36)	0.08 (-0.09, 0.24)
BMI-for-age z-score at Week 96	-0.18 (-0.64, 0.28)	0.14 (-0.08, 0.36)
Weight (kg) at Week 96	4.2 (3.7, 4.7)	4.7 (4.2, 5.2)
Stature (cm) at Week 96	13.2 (12.1, 14.3)	13.1 (12.3, 14.0)
BMI (kg/m^2) at Week 96	-0.25 (-0.71, 0.21)	0.07 (-0.27, 0.41)
Markers of Pancreatic Function and Intestinal Inflammation		
IRT (µg/L) through Week 96	NA	-86.1 (-182.6, 10.4)
FE-1 (mg/kg) through Week 96	NA	48.7 (14.2, 83.2)
Fecal calprotectin (mg/kg) through Week 96	NA	-123.61 (-232.93, -14.30)

Sources: Tables 14.2.1.1f, 14.2.1.2f, 14.2.1.3f, 14.2.2.1f, 14.2.2.2f, 14.2.3.1f, 14.2.4.1f, 14.2.5.1f, 14.2.6.1f, 14.2.7.1f, 14.2.8.1f, 14.2.10.1f, 14.2.12.1f, 14.2.13.1f, and 14.2.14.1f

BMI: body mass index; FE-1: fecal elastase-1; IRT: immunoreactive trypsinogen; LCI: lung clearance index; $LCI_{5.0}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value; LUM/IVA: lumacaftor/ivacaftor; MRI: magnetic resonance imaging; N: total sample size; NA: not applicable; PBO: placebo

Note: Study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in Part 1. Through Week 96 was defined as the average of all post-baseline measures at scheduled visits up to Week 96. As such, the continuous endpoints from baseline through Week 96 were only applicable to the LUM/IVA-LUM/IVA group.

Results on additional endopoints

Numerical improvements were also observed after LUM/IVA treatment for other additional continuous endpoints, based on within-group changes from baseline at or through Week 48, including MRI outcomes (i.e., reduction in scores), LCI5.0, additional growth parameters, and markers related to pancreatic function and intestinal inflammation.

For subjects who received LUM/IVA in both Parts 1 and 2 (LUM/IVA-LUM/IVA group), these numerical improvements were generally sustained in Part 2, demonstrating the clinical benefit of LUM/IVA treatment over a cumulative period of 96 weeks. For subjects who initiated LUM/IVA in Part 2 (placebo-LUM/IVA group), the numerical improvements in efficacy outcomes observed after 48 weeks of LUM/IVA treatment were consistent with those observed in Part 1.

Safety results

The majority of subjects had AEs that were considered mild (LUM/IVA: 28.6%; placebo: 37.5%) or moderate (LUM/IVA: 68.6%; placebo: 62.5%) in severity (Table 12-1.). One subject in the LUM/IVA group had a severe AE (ALT increased). No subjects had life-threatening AEs. No subjects had an AE

that led to study drug discontinuation. Three (8.6%) subjects had AEs that led to LUM/IVA interruption (autoimmune hepatitis, intussusception, and increased AST). No AEs led to placebo interruption. A total of 7 (20.0%) subjects in the LUM/IVA group and 2 (12.5%) subjects in the placebo group had SAEs; none were considered related or possibly related to study drug. No subjects had AEs leading to death.

Table 12-1 Part 1: Overview of AEs (Safety Set)

	n (%)		
Category	**PBO N = 16**	**LUM/IVA N = 35**	**Total N = 51**
Number of AEs (total)	126	214	340
Subjects with any AEs	16 (100.0)	35 (100.0)	51 (100.0)
Subjects with AEs by maximum severity			
Mild	6 (37.5)	10 (28.6)	16 (31.4)
Moderate	10 (62.5)	24 (68.6)	34 (66.7)
Severe	0	1 (2.9)	1 (2.0)
Life-threatening	0	0	0
Subjects with AEs by relationship			
Not related	4 (25.0)	13 (37.1)	17 (33.3)
Unlikely related	4 (25.0)	9 (25.7)	13 (25.5)
Possibly related	8 (50.0)	13 (37.1)	21 (41.2)
Related	0	0	0
Subjects with AEs leading to study drug discontinuation	0	0	0
Subjects with AEs leading to study drug interruption	0	3 (8.6)	3 (5.9)
Subjects with SAEs	2 (12.5)	7 (20.0)	9 (17.6)
Subjects with related SAEs	0	0	0
Subjects with AEs leading to death	0	0	0

Sources: Table 14.3.1.1p and Table 14.3.2.3.3p

AE: adverse event; IVA: ivacaftor; LUM: lumacaftor; n: size of subsample; N: total sample size; PBO: placebo; SAE: serious adverse event

Notes: Events were coded with MedDRA Version 23.1. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing the number of subjects with related SAEs, SAEs with relationship of related, possibly related, or missing were counted.

The most common SOCs (≥30% incidence overall) in which AEs were reported were infections and infestations; gastrointestinal disorders; and respiratory, thoracic, and mediastinal disorders (see Table 12-2).

Table 12-2 Part 1: Adverse Events Occurring in At Least ≥10% of Subjects in Any Treatment Group by Preferred Term (Safety Set)

Preferred Term[a]	PBO N = 16 n (%)	LUM/IVA N = 35 n (%)
Any adverse event	16 (100.0)	35 (100.0)
Nasopharyngitis	8 (50.0)	22 (62.9)
Infective PEx of CF	9 (56.3)	16 (45.7)
Rhinitis	6 (37.5)	9 (25.7)
Gastroenteritis	2 (12.5)	3 (8.6)
Upper respiratory tract infection	3 (18.8)	1 (2.9)
Bacterial disease carrier	2 (12.5)	0
Abdominal pain	2 (12.5)	7 (20.0)
Constipation	0	4 (11.4)
Diarrhoea	1 (6.3)	4 (11.4)
Vomiting	2 (12.5)	2 (5.7)
Abdominal pain upper	2 (12.5)	1 (2.9)
Faeces pale	2 (12.5)	0
Cough	5 (31.3)	10 (28.6)
Epistaxis	2 (12.5)	2 (5.7)
Dyspnoea	2 (12.5)	1 (2.9)
Nasal polyps	2 (12.5)	1 (2.9)
Nasal congestion	4 (25.0)	0
Productive cough	2 (12.5)	0
Pyrexia	3 (18.8)	6 (17.1)
Pseudomonas test positive	2 (12.5)	1 (2.9)
Headache	2 (12.5)	3 (8.6)

Source: Table 14.3.1.2p

AE: adverse event; CF: cystic fibrosis; IVA: ivacaftor; LUM: lumacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term

Note: MedDRA Version 23.1. Table is sorted in descending order of frequency of the LUM/IVA column by PT.

[a] PTs were provided only for AEs that occurred in ≥10% of subjects in any treatment group. A subject with multiple events within a PT was counted only once within the PT.

AEs were generally consistent with common manifestations and complications of CF in this young age group. The most common AEs (≥20% incidence) in both treatment groups by PT were nasopharyngitis (LUM/IVA: 62.9%; placebo: 50.0%), infective PEx of CF (LUM/IVA: 45.7%; placebo: 56.3%), cough (LUM/IVA: 28.6%; placebo: 31.3%), and rhinitis (LUM/IVA: 25.7%; placebo: 37.5%).

Overall, the majority of subjects had AEs that were considered mild (16 [31.4%] subjects) or moderate (34 [66.7%]) in severity. One subject in the LUM/IVA group had a severe AE of increased ALT that was considered unlikely related to study drug and resolved without any change in study drug dose. No severe AEs were reported in the placebo group. No subjects in either treatment group had life-threatening AEs.

Relationship of AEs

The incidence of AEs considered related to study drug is presented in Table 12-3. The most common (occurring in ≥8% subjects) related AEs in the LUM/IVA group were abdominal pain and cough. The most common (occurring in ≥12% subjects) related AEs in the placebo group were upper abdominal pain and nasal congestion. All other related AEs occurred in 1 subject each, except for diarrhea.

Table 12-3 Part 1: Subjects With Related Adverse Events by Preferred Term (Safety Set)

Preferred Term[a]	PBO N = 16 n (%)	LUM/IVA N = 35 n (%)
Subjects with any related[b] AEs	8 (50.0)	13 (37.1)
Abdominal pain	1 (6.3)	4 (11.4)
Diarrhoea	0	2 (5.7)
Faeces discoloured	0	1 (2.9)
Frequent bowel movements	1 (6.3)	1 (2.9)
Abdominal pain upper	2 (12.5)	0
Abnormal faeces	1 (6.3)	0
Post-tussive vomiting	1 (6.3)	0
Cough	1 (6.3)	3 (8.6)
Bronchospasm	0	1 (2.9)
Sputum increased	0	1 (2.9)
Tachypnoea	0	1 (2.9)
Dyspnoea	1 (6.3)	0
Nasal congestion	2 (12.5)	0
Nasal obstruction	1 (6.3)	0
Wheezing	1 (6.3)	0
Rash	0	1 (2.9)
Hyperhidrosis	0	1 (2.9)
Fatigue	0	1 (2.9)
Autoimmune hepatitis	0	1 (2.9)
Infective PEx of CF	1 (6.3)	0
Upper respiratory tract infection	1 (6.3)	0
Headache	1 (6.3)	0

Source: Table 14.3.1.8p
AE: adverse event; CF: cystic fibrosis; IVA: ivacaftor; LUM: lumacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term
Note: MedDRA Version 23.1.
[a] If a subject had multiple events within a PT, the subject was counted only once under the strongest relationship in that category.
[b] Related included either possibly related or related study drug categories.

AESIs of Respiratory Events and Elevated Transaminases

Respiratory events and elevated transaminases were the adverse events of special interest (AESIs).

Two (5.7%) subjects on LUM/IVA and 3 (18.8%) subjects in the placebo group had at least 1 AESI of respiratory events, all of which were mild or moderate in severity. No serious AESIs of respiratory events occurred, and no AESI of respiratory events led to treatment discontinuation or interruption.

Three (8.6%) subjects on LUM/IVA had at least 1 AESI of elevated transaminases. For 1 subject, treatment was interrupted due to the event (AST increased). None of the AESIs of elevated transaminases were serious and none led to treatment discontinuation. No subjects in the placebo group had AESIs of elevated transaminases.

Deaths, Other Serious AEs, and Other Significant AEs

There were no deaths in Part 1.

A total of 7 (20.0%) subjects in the LUM/IVA group and 2 (12.5%) subjects in the placebo group had at least 1 SAE. Three (8.6%) subjects in the LUM/IVA group and 1 (6.3%) subject in the placebo group had an SAE of infective PEx of CF, which is a common manifestation of CF disease. The other SAEs included pneumonia, constipation, hematemesis, and intussusception in the LUM/IVA group and lung infiltration in the placebo group (in 1 subject each).

None of the SAEs were considered related to study drug The SAE of intussusception led to study drug interruption; study drug dose was not changed for any other SAEs. All SAEs had an outcome of resolved, except lung infiltration that was ongoing at the time of this report.

Table 12-4 Part 1: SAEs by PT (Safety Set)

	n (%)	
Preferred Term	PBO N = 16	LUM/IVA N = 35
Subjects with any SAEs	2 (12.5)	7 (20.0)
Infective PEx of CF	1 (6.3)	3 (8.6)
Pneumonia	0	1 (2.9)
Constipation	0	1 (2.9)
Haematemesis	0	1 (2.9)
Intussusception	0	1 (2.9)
Lung infiltration	1 (6.3)	0

Source: Table 14.3.2.2p

CF: cystic fibrosis; IVA: ivacaftor; LUM: lumacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

Notes: MedDRA Version 23.1 was used. A subject with multiple events within a category was counted only once in that category. The table is sorted in descending order of the LUM/IVA column by SOC and by PT within each SOC.

AEs That Led to Discontinuation or Interruption of Study Drug

No AEs led to discontinuation of study drug in either treatment group.

Three (8.6%) subjects each had 1 AE that led to LUM/IVA interruption as follows:

• One subject had moderate intussusception that worsened to serious, was unlikely related to study drug, and resolved with treatment after 12 days.

• One subject had mild increased AST that was unlikely related to study drug and resolved after 17 days.

• One subject had an AE of moderate autoimmune hepatitis on Study Day 200 that was considered possibly related to LUM/IVA by the investigator; the event resolved after 50 days. Before and during the event, the subject had ALT elevations >5 × ULN but <8 × ULN, and AST elevations <3 × ULN; the subject had no clinical signs or symptoms of autoimmune hepatitis. After resolution of the event and resumption of study drug, ALT remained <5 × ULN for the rest of the study and was mostly <3 × ULN. Vertex assessed the event as more consistent with CF liver disease because the autoimmune hepatitis was not supported by biopsy, positive antibodies are common in the general population, and the subject had a rapid resolution of the transaminase elevations without steroid treatment, with a negative response to LUM/IVA rechallenge.

2.3.2. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) No1901/2006, the MAH has submitted the results of Study 121.

The present study was designed to explore the long-term disease progression and efficacy of LUM/IVA in subjects 2 through 5 years of age, homozygous for F508del in a placebo-controlled setting, with a window of opportunity to halt disease progression and prevent organ damage by early intervention with therapies that treat the underlying cause of CF.

This is an exploratory Phase 2, randomized, double-blind, placebo-controlled, multicentre study designed to explore the impact of LUM/IVA on disease progression in subjects aged 2 through 5 years with Cystic fibrosis (CF), homozygous for F508del.

The duration of 48 weeks of placebo-controlled treatment in Part 1, plus an additional 48 weeks of open-label LUM/IVA treatment in Part 2, was expected to provide an adequate assessment of efficacy and safety, including long-term impact on disease progression, in particular, structural damage assessed via MRI.

Almost all subjects enrolled in Part 1 completed (100% in the PBO and 94.3% in the LUM/IVA arm) so that only 2 subjects discontinued early. Same figure is observed for the part 2 (100% in the PBO arm and 97% in the LUM/IVA arm: with only 2 subjects discontinued LUM/IVA treatment (both due to AEs) and 1 (2.0%) subject discontinued the study.

With regard to baseline characteristics, the majority of subjects (64.7%) were male, and the mean age at baseline was 4.2 years.

Study results showed an overall trend of a numerical improvement in LUM/IVA arm as compared to PBO arm across the different endpoints. The primary endpoint was change from baseline in MRI global chest score at Week 48. Based on Bayesian posterior probability, the probability of LUM/IVA was 76.23%. superior to placebo. The mean (95% CI) difference between LUM/IVA and placebo was -1.5 (-5.5, 2.6).

Results from the secondary endpoint (absolute Change in LCI2.5 From Baseline at Week 48 showed a numerical improvement (i.e., a reduction) in LCI2.5 in the LUM/IVA arm with a mean (95% CI) absolute change from baseline of -0.37 (-0.85, 0.10) through Week 48.

Looking at the growth parameters i.e. absolute Change in Weight-for-age Z-score/ Stature-for-age Z-score/ Body Mass Index-for-Age Z-score at Week 48 the results were consistent across the three different endpoints showing a numerical improvement in the LUM/IVA arm and a (slight) decrease in the PBO arm for weight-for-age and BMI-for-age z-scores.

Regarding the safety profile, no new safety concerns have been identified and the known AEs were reported. The majority of AEs were mild or moderate in severity. The most common were nasopharyngitis, infective PEx of CF, cough, and rhinitis. There were no deaths. The SAEs were considered to be not related or unlikely related to study drug by study investigators. AESIs, including respiratory events and elevated transaminases, were infrequent, 1 led to treatment discontinuation. Of note, no important impact on laboratory findings has been observed and no subjects had a cataract.

Overall, data coming from Study 121 support the B/R risk on LUM/IVA for the subjects 2 through 5 years of age, homozygous for F508del.

3. CHMP overall conclusion and recommendation

Overall, data coming from Study 121 support the B/R risk on LUM/IVA for the subjects 2 through 5 years of age, homozygous for F508del.

■ Fulfilled:

No regulatory action required.