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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/P46/012

Note

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

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Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Orkambi

International non-proprietary name: Lumacaftor/Ivacaftor

Procedure no.: EMEA/H/C/003954/P46 012

Marketing authorisation holder: Vertex Pharmaceuticals (Europe) Limited

Rapporteur:	UK
Start of the procedure:	02/04/2018
Date of this report:	24/05/12
Deadline for CHMP member's comments:	
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1. Introduction

On 19/03/2018, the MAH submitted a completed paediatric study for Orkambi (Lumacaftor/Ivacaftor), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted a study titled 'A Phase 2, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects with Cystic Fibrosis Who Have an A455E-CFTR Mutation.

This Study No: VX15-809-111 (Study 111) is submitted as a stand-alone, post-authorization measure (PAM) under Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation').

The A455E mutation results in a severe reduction of mature CFTR protein at the cell surface. Results of in vitro studies suggest that A455E-CFTR could be rescued by the same strategies as F508del-CFTR (in vitro strategies include cell co-transfection or incubation with chemical correctors). In turn, these findings suggested that A455E might be a suitable candidate for LUM/IVA treatment

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a clinical study report for:

'A Phase 2, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation.

2.2.2. Clinical study

A Phase 2, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation.

Study No: VX15-809-111

Description

Study VX15-809-111 is being submitted under Article 46 of Regulation (EC) No 1901/2006 as a stand-alone post authorisation measure.

Primary Objective

To evaluate the efficacy of LUM/IVA in subjects with CF 12 years of age and older who have at least one *A455E* mutation.

Other Objectives

- To explore the association between LUM/IVA-induced CFTR function in in vitro organoid-based measurements and clinical response to LUM/IVA in subjects with CF 12 years of age and older who have at least one *A455E* mutation.
- To explore the effect of LUM/IVA on glucose tolerance and insulin secretion in subjects with CF 12 years of age and older who have at least one *A455E* mutation.

Rationale for this study:

Cystic fibrosis (CF) is caused by reduced quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in multiple organs.1 In people with CF, decreased CFTR chloride transport results in multisystem pathology. Although the disease affects multiple organs, progressive loss of lung function is the leading cause of mortality.

Lumacaftor (LUM) is a CFTR corrector that increases the quantity of CFTR delivered to the cell surface, and ivacaftor (IVA) is a CFTR potentiator that increases the channel gating activity of CFTR at the cell surface. The *A455E-CFTR* mutation is reported to occur in less than 0.1% of patients with CF worldwide, but large regional differences in prevalence exist. In the Netherlands, it is the second most prevalent mutation, occurring in 3.6% of all patients with CF, with even higher prevalence in some areas.5 Although the *A455E* mutation was initially reported to be associated with mild lung disease6, current clinical experience shows marked differences in clinical disease severity, ranging from relatively mild to severe loss of lung function at young adulthood.

The *A455E* mutation results in a severe reduction of mature CFTR protein at the cell surface.

Results of in vitro studies suggest that A455E-CFTR could be rescued by the same strategies as F508del-CFTR (in vitro strategies include cell co-transfection or incubation with chemical correctors). In turn, these findings suggested that *A455E* might be a suitable candidate for LUM/IVA treatment.

A novel functional CFTR assay has been established using patient-derived intestinal stem cell cultures termed organoids. Organoids have crypt-like structures and an internal lumen lined by differentiated cells, recapitulating the in vivo tissue architecture, with intestinal CFTR expressed at the apical membrane. CFTR activation by forskolin (which increases cyclic AMP levels) drives CFTR-dependent chloride secretion, inducing rapid, measurable swelling of organoids.

In this in vitro model, organoids derived from patients homozygous for *F508del* displayed less forskolin-induced swelling than organoids derived from healthy controls.8 Incubation of the *F508del/F508del* organoids with LUM/IVA enhanced forskolin-induced swelling, and a similar LUM/IVA-induced improvement was observed in *A455E/F508del* organoids. Based on the in vitro findings, it is hypothesized that LUM/IVA treatment can increase CFTR function and improve disease parameters in patients with CF who have an *A455E* mutation.

Methods

Objective(s)

Primary Objective

To evaluate the efficacy of lumacaftor (LUM)/ivacaftor (IVA) in subjects with cystic fibrosis (CF) 12 years of age and older who have at least one *A455E* mutation.

Other Objectives

- To explore the association between LUM/IVA-induced CFTR function in in vitro organoid-based measurements and clinical response to LUM/IVA in subjects with CF 12 years of age and older who have at least one *A455E* mutation.
- To explore the effect of LUM/IVA on glucose tolerance and insulin secretion in subjects with CF 12 years of age and older who have at least one *A455E* mutation

Study design

A crossover design with a 1:1 randomization to the 2 treatment sequences enabled within-subject comparisons of the effects of placebo and LUM/IVA. The use of placebo was necessary in order to provide a robust assessment in this small number of subjects.

Study Drug Dose and Duration

Dose of LUM and IVA

The L400/I250 every 12 hours (q12h) dose regimen was approved in the US, EU, Canada,

Australia, Switzerland, and Israel for the treatment of CF in patients 12 years of age and older who are homozygous for F508del.

Duration of Dosing

The 8-week dosing duration in each treatment period was chosen based on results of the pivotal, placebo-controlled, Phase 3 studies (Studies 103 and 104), in which the effect of LUM/IVA therapy was assessed in CF subjects homozygous for F508del. These studies showed an improvement in percent predicted forced expiratory volume in 1 second (ppFEV1) after 8 weeks of treatment.

Washout Period

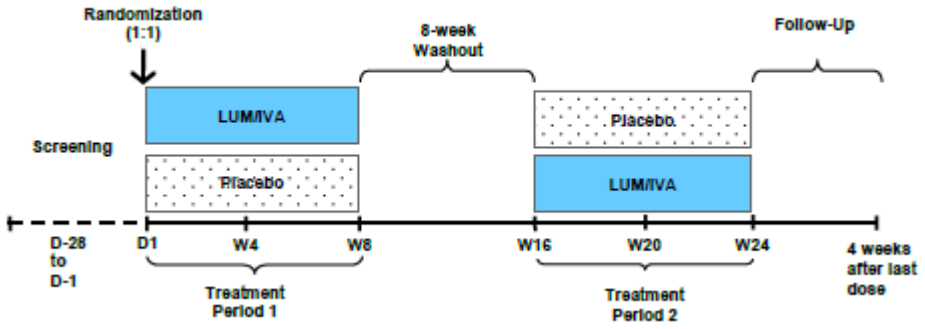
An 8-week period was selected as the duration for the Washout Period. It was expected that some subjects would be on 28-day-on/28-day-off cycles of stable CF medication. An 8-week washout period is compatible with these cycles.

Inclusion: Male and female subjects 12 years of age and older with confirmed CF, with an A455E mutation on at least 1 CFTR allele, and with forced expiratory volume in 1 second (FEV1) ≥30% of predicted and ≤90% of predicted at screening.

Approximately 20 subjects were planned to be randomized 1:1 to the 2 treatment sequences: LUM/IVA followed by placebo (Sequence 1) or placebo followed by LUM/IVA (Sequence 2).

An interactive web or voice response system was used to assign subjects to treatment sequences in a 1:1 ratio to receive either LUM/IVA during Treatment Period 1 and placebo during Treatment Period 2 (Sequence 1) or placebo during Treatment Period 1 and LUM/IVA during Treatment Period 2 (Sequence 2).

Figure 2-1 Study Design



A schematic of the study design is provided in Figure 2-1.

Study population /Sample size

Inclusion Criteria

Subjects who met all of the following inclusion criteria were eligible:

1. Male or female with confirmed diagnosis of CF. The subject had **both** of the following:

- One or more characteristic phenotypic features, such as chronic cough and sputum production, persistent chest radiograph abnormalities, **or** airway obstruction manifested by wheezing and air trapping; **or** a history of CF in a sibling; **or** a positive newborn screening test result;
- An increased sweat chloride concentration by pilocarpine iontophoresis on 2 or more occasions; **or** identification of 2 CF mutations; **or** demonstration of abnormal nasal epithelial ion transport.

2. Age 12 years or older on the date of informed consent.

3. *A455E* mutation on at least 1 *CFTR* allele.

4. Forced expiratory volume in 1 second (FEV1) ≥30% of predicted and ≤90% of predicted at the Screening Visit, based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations.

5. Stable CF disease as judged by the investigator.

6. Willing to remain on a stable medication regimen for CF from 4 weeks before Day 1 through the Follow-up Visit.

7. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.

8. Subject (or subject's legally appointed and authorized representative) signed and dated an ICF, and where appropriate, assent form

Treatments

Table 9-2 Study Drug

Drug Name	Lot Numbers	Dosing Form/Route	How Supplied	Storage Condition
LUM/IVA	6054025 B16141	Fixed-dose tablet/Oral	Supplied as 200-mg LUM/125-mg IVA tablets	≤30°C (86°F)
Placebo	B14113 B16129	Tablet/Oral	No active drug	≤30°C (86°F)

IVA: ivacaftor; LUM: lumacaftor
Notes: The appearance of the placebo was matched to the LUM/IVA tablets.

Treatments administered to participants randomised to sequences as indicated in table 9.1

Blinding: This study was double-blind.

Duration of treatment: 8 weeks (seq 1) + 8 weeks (washout) + 8 weeks (seq 2)

Outcomes/endpoints

Efficacy Assessments

Primary efficacy assessment: Spirometry (excluding assessments on Day 2 and the day after the Week 16 Visit [if applicable]);

Others:

Sweat chloride; Cystic Fibrosis Questionnaire-Revised (CFQ-R); weight and body mass index (BMI); height- and weight-for-age and BMI-for-age z-scores (for subjects less than 21 years of age); and documentation of events related to outcome (e.g., pulmonary exacerbations).

Safety Assessments

Adverse events (AEs), clinical laboratory assessments (liver function tests [LFTs]), ophthalmologic examinations (OEs) (for subjects less than 18 years of age), vital signs, and spirometry (on Day 2 and the day after the Week 16 Visit only, for subjects with FEV1 <40% of predicted).

Exploratory Assessments

In vitro analysis of LUM/IVA-induced CFTR function using an organoid assay; glucose and insulin levels in oral glucose tolerance test (OGTT).

Statistical Methods

No formal sample size calculation was conducted for this study. The planned sample size was based on the number of subjects expected to be available for participation.

Efficacy analyses were based on the FAS, which was defined as all randomized subjects who had at least one *A455E* mutation and received at least 1 dose of study drug. Safety analyses were based on the Safety Set. Data for a period were used if the subject received at least 1 dose of study drug in that treatment period.

The study baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the study. The period baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in each treatment period.

Statistical inferences for efficacy analyses were based on change from study baseline unless otherwise stated.

Efficacy Analyses

The primary efficacy endpoint was the absolute change in percent predicted FEV1 (ppFEV1) from study baseline through 8 weeks of treatment. The primary analysis of the primary endpoint was based on a mixed-effects model for repeated measures (MMRM) that included the absolute change from the study baseline in each treatment period as the dependent variable, with sequence, treatment, period, visit within period, and treatment-by-visit interaction as fixed effects, study baseline ppFEV1 as a covariate, and subject nested within sequence as a random effect. Visit was treated as a class variable. An unstructured covariance matrix was assumed for the repeated measurements of the same subject within each treatment period. The denominator degrees of freedom for the F-test for fixed effects was estimated using the Kenward-Roger approximation.

The estimated mean treatment difference overall (through Week 8) and its corresponding 95% CI and 2-sided *P* value were provided. The estimated mean treatment difference at each visit and its corresponding 95% CI and *P* value were also presented. The raw values and changes from baseline were summarized by treatment using descriptive statistics at each scheduled visit.

As a supportive sensitivity analysis, the MMRM analysis was repeated using change from period baseline instead of change from study baseline.

Safety Analyses

The incidence of treatment-emergent AEs (TEAEs) was summarized in contingency tables by treatment. For clinical laboratory assessments, vital signs, and pulse oximetry (only for subjects with ppFEV1 <40 at screening), the raw values and changes from period baseline were summarized by treatment. The incidence of subjects with at least 1 assessment meeting threshold criteria during the TE Period was summarized for LFTs.

Results

Recruitment / Number analysed

All 20 randomized subjects completed dosing in Treatment Period 1, and 17 (85.0%) subjects completed dosing in Treatment Period 2 and completed the study. No subjects discontinued during the TE periods; 3 discontinuations occurred during the Washout Period.

Demographics and Other Baseline Characteristics

All subjects were White. The majority of subjects were female (60.0%), and the median age was 40.0 years, with 18 (90.0%) subjects being ≥18 years of age. Two subjects were between 12-18y of age. The mean (SD) ppFEV1 was 58.9 (15.3), with 2 (10.0%) subjects having a ppFEV1 <40. Means and distributions for each demographic and other baseline characteristic were generally similar between the 2 treatment sequence groups. The common medical history conditions and prior and concomitant medications used were consistent with those of a CF population.

Efficacy results

Evaluation of efficacy was the primary objective of this double-blind, placebo-controlled, crossover study of LUM/IVA in CF subjects 12 years of age and older with at least one A455E-CFTR mutation. The study was exploratory in nature, and no power calculations were made due to the limited number of subjects with this rare mutation that is prevalent in the Netherlands.

☐ The primary endpoint, absolute change in ppFEV1 from study baseline through 8 weeks of treatment, was not met; there was no treatment difference between placebo and LUM/IVA.

Table 11-1 MMRM Analysis of Absolute Change From Study Baseline in $ppFEV_1$ Through Week 8, FAS

Statistic	Placebo N = 18	L400/I250 q12h N = 19
Study baseline		
n	18	19
Mean (SD)	59.4 (15.9)	57.6 (14.6)
Absolute change through Week 8		
n	18	18
LS mean (SE)	2.6 (1.2)	2.7 (1.1)
95% CI of LS mean	(0.2, 4.9)	(0.3, 5.0)
P value within treatment	0.0340	0.0272
LS mean difference (95% CI)	NA	0.1 (-2.5, 2.7)
P value versus placebo	NA	0.9277

• In a prespecified sensitivity analysis of absolute change in ppFEV1 from period baseline, the least squares (LS) mean treatment difference between LUM/IVA and placebo through 8 weeks of treatment was 2.1 percentage points (P = 0.1169).

☐ Other efficacy endpoints supported or were suggestive of the potential clinical benefit of LUM/IVA. Through Week 8, the LS mean treatment difference between LUM/IVA and placebo was as follows:

o Sweat chloride concentration: -7.8 mmol/L (P = 0.0037)

o CFQ-R respiratory domain: 3.5 (P = 0.4691)

☐ The in vitro organoid-based assay performed as expected; increased LUM/IVA concentration was associated with increased organoid swelling. However, no conclusions were drawn from the exploratory analysis of organoid based in vitro measurements versus clinical outcomes due to the limited and unbalanced sample size of subjects across mutation groups.

☐ No meaningful treatment differences were observed in the OGTT endpoints, and based on the baseline data, there did not appear to be impaired glucose tolerance among study subjects.

Safety Results

☐ Administration of LUM 400 mg q12h/IVA 250 mg q12h for approximately 8 weeks was safe and well-tolerated in subjects with CF. No new safety concerns were identified.

☐ The incidence of AEs was 72.2% while receiving placebo and 78.9% while receiving LUM/IVA. One subject had a severe AE of hypertension while receiving LUM/IVA. All other AEs were mild or moderate in severity.

☐ By Preferred Term, the most common AEs occurred only while receiving LUM/IVA and were diarrhea (42.1%), flatulence (21.1%), nausea (21.1%), and headache (21.1%).

☐ The incidence of related AEs was 22.2% while receiving placebo and 36.8% while receiving LUM/IVA. The most common related AEs were diarrhea and flatulence, which occurred during LUM/IVA treatment only, and sputum increased, which occurred at similar incidences during both placebo (11.1%) and LUM/IVA (10.5%) treatment.

☐ No subjects had AEs that led to treatment discontinuation or interruption.

☐ No deaths or serious AEs occurred.

☐ No important trends were identified from chemistry, hematology, vital signs, physical examinations, or OEs. No subjects had alanine transaminase or aspartate transaminase elevations >3 × upper limit of normal or any bilirubin elevations.

2.2.3. Discussion on clinical aspects

Study VX15-809-111 was a randomised crossover study. Evaluation of efficacy was the primary objective of this study. The study was exploratory in nature, and no power calculations were made due to the limited number of subjects with this rare mutation that is prevalent in the Netherlands.

The primary endpoint, absolute change in ppFEV1 from study baseline through 8 weeks of treatment, was not met and showed no treatment difference between placebo and LUM/IVA.

This outcome is consistent with the small sample size of the study combined with the known variability of ppFEV1 measurements.

Lung function, as measured by spirometry (ppFEV1), is a well-established endpoint in studies of therapies for CF. In a prespecified sensitivity analysis of absolute change in ppFEV1 from period baseline, the LS mean treatment difference between LUM/IVA and placebo through 8 weeks of treatment was 2.1 percentage points (P = 0.1169).

Sweat chloride is a direct in vivo measure of CFTR function. Subjects had a statistically significant improvement (i.e., a reduction) in sweat chloride concentration while receiving LUM/IVA but not while receiving placebo. Through Week 8, the LS mean treatment difference between LUM/IVA and placebo in sweat chloride concentration was -7.8 mmol/L (*P* = 0.0037).

Intestinal-like organoid swelling is a measure of CFTR function in vitro, and in this study, it was compared with clinical outcomes (ppFEV1 and sweat chloride) as an exploratory analysis. The in vitro organoid-based assay performed as expected; increased LUM/IVA concentration was associated with increased organoid swelling. However, no conclusions were drawn from the exploratory analysis of organoid-based in vitro measurements versus clinical outcomes due to the limited and unbalanced sample size of subjects across mutation groups.

A time course of glucose and insulin levels was evaluated as an exploratory endpoint. No meaningful treatment differences were observed in the OGTT endpoints. Based on the baseline data, there did not appear to be impaired glucose tolerance among study subjects.

Safety: Administration of L400/I250q12h for approximately 8 weeks was safe and well-tolerated in subjects with CF. No new safety concerns were identified.

The incidence of AEs was 72.2% while receiving placebo and 78.9% while receiving LUM/IVA.

One subject had a severe AE of hypertension while receiving LUM/IVA. All other AEs were mild or moderate in severity.

By PT, the most common AEs occurred only while receiving LUM/IVA and were diarrhea

(42.1%), flatulence (21.1%), nausea (21.1%), and headache (21.1%).

The incidence of related AEs was 22.2% while receiving placebo and 36.8% while receiving LUM/IVA. The most common related AEs were diarrhea and flatulence, which occurred during LUM/IVA treatment only, and sputum increased, which occurred at similar incidences during both placebo (11.1%) and LUM/IVA (10.5%) treatment.

No subjects had AEs that led to treatment discontinuation or interruption.

No deaths or SAEs occurred.

No important trends were identified from chemistry, hematology, vital signs, PEs, or OEs. No subjects had ALT or AST elevations >3 × ULN or any bilirubin elevations.

Overall, the safety results were consistent with the known safety profile of LUM/IVA.

3. Rapporteur's overall conclusion and recommendation

This Phase 2, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation was an unpowered exploratory study to evaluate the efficacy of lumacaftor (LUM)/ivacaftor (IVA) in subjects with cystic fibrosis (CF) 12 years of age and older who have at least one *A455E* mutation. Two of 17 subjects in this study were between the ages of 12-18years.

While the primary efficacy outcome was not met, no new safety issues were identified with regard to Orkambi.

☒ Fulfilled:

No regulatory action required. The applicant has not suggested any updates to the product information for Orkambi.