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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/P46/013

Note

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

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

Orkambi 100mg/125mg film-coated tablet

Lumacaftor/ivacaftor

EMEA/H/C/003954/P46/013

Applicant: Vertex Pharmaceuticals Ltd.

CHMP Rapporteur:	**Nithyandan Nagercoil**
Start of the procedure:	**30 April 2018**

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	anaerobic threshold
AUC	area under the concentration versus time curve
AUC_T	AUC during a dosing interval
βhCG	beta-human chorionic gonadotrophin
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFRD	CF related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CRF	case report form
CSR	clinical study report
CYP	cytochrome P450
DEXA	dual-energy X-ray absorptiometry
DIOS	distal intestinal obstruction syndrome
DOF	degrees of freedom
ECG	electrocardiogram
EDC	electronic data capture
ETT	early termination of treatment
EU	European Union
FDA	Food and Drug Administration
FDC	fixed-dose combination
F508del-CFTR	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del-CFTR	CFTR protein with a deletion of phenylalanine corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FEV_1	forced expiratory volume in 1 second
FH	fasting hyperglycaemia
FVC	forced vital capacity
GAD-7	Generalised Anxiety Disorder
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
HbA1c	glycosylated haemoglobin

ICH	International Conference on Harmonization
IGT	impaired glucose tolerance
INDET	interdeterminate glucose tolerance
IVA	ivacaftor
LFT	liver function test
LLN	lower limit of normal
Ls	least squares
LUM	lumacaftor
LUM/IVA	lumacaftor in combination with ivacaftor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
NGT	normal glucose tolerance
OE	ophthalmological examination
OGTT	oral glucose tolerance test
PEx	pulmonary exacerbation
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PHQ-8	Patient Health Questionnaire
PR	PR interval, segment
q12h	every 12 hours
QTcB	QT interval corrected by Bazett's formula
RML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
VCO_2	carbon dioxide production
VO_2	oxygen consumption
VE	pulmonary ventilation
VO_{2max}	maximal oxygen consumption
WHO-DDE	World Health Organization Drug Dictionary Enhanced

Recommendation

1. Introduction

Study VX15-809-112 (Study 112) is submitted as a stand-alone post-authorisation measure under Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation').

The study was a Phase IV, Randomised, Double-blind, Placebo-controlled, Parallel-design Study of the Effect of Lumacaftor/Ivacaftor Combination Therapy on Exercise Tolerance in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

The study was initiated 14 September 2016 (date first eligible subject signed the informed consent/assent form) and was completed 23 October 2017 (date last subject completed the last visit)

CHMP comment

The submission was received on 13th April, within 6 months of study completion, in accordance with the regulation.

2. Scientific discussion

Study VX15-809-112 (Study 112) was designed to evaluate the effect of LUM/IVA on exercise tolerance in subjects with cystic fibrosis (CF). Exercise capacity, as measured by maximal oxygen consumption (VO2max) during cardiopulmonary exercise testing (CPET), has been demonstrated to be a significant predictor of mortality in patients with CF. A small randomised crossover study and published case series suggest that IVA may improve VO_{2max} and other measures of exercise capacity. These findings may be independent of improvements in forced expiratory volume in 1 second (FEV1) previously demonstrated with IVA. At the time the Study 112 protocol was developed, there had been no prospective randomised evaluation of LUM/IVA effects on exercise capacity as measured by CPET. Selected sites also participated in a body composition substudy, a glucose tolerance substudy, or both; exercise training is known to change body composition and increase glucose tolerance.

2.1. Clinical aspects

2.1.1. Introduction

LUM/IVA combination therapy is approved as Orkambi™ for the treatment of CF in patients 6 years of age and older, homozygous for F508del in the US, Canada, and EU and for CF patients 12 years of age and older, homozygous for F508del in Australia, Switzerland, and Israel (indication extension applications to include patients 6 through 11 years of age are pending in these regions). Applications to extend the indication to CF patients 2 through 5 years of age are also pending in the US, Canada, and EU.

Vertex initiated a postmarketing study on exercise tolerance (Study 112) in CF subjects aged 12 years and older, homozygous for F508del. In Study 112, several measures of exercise tolerance and aerobic fitness were evaluated based on CPET. In addition, conventional CF endpoints were evaluated for the impact of exercise tolerance and training on manifestations of CF. Actigraphy-based evaluations of activity and sleep levels provided a further measure of health. Questionnaires were used to assess the presence of depression and anxiety symptoms. In a body composition substudy, body composition and bone mineral density changes were measured by dual-energy X-ray absorptiometry (DEXA). In a

glucose tolerance substudy, the effect of CFTR modulation on the subjects' pancreatic endocrine function, as measured by glucose levels in the oral glucose tolerance test (OGTT), was explored.

Information on the pharmaceutical formulation used in the study

Formulation and Composition

- 200-mg LUM/125-mg IVA film-coated FDC tablets
- 0-mg LUM/0-mg IVA placebo film-coated tablets

Dose Regimen

Approximately 66 subjects were planned to be randomized 1:1 to the following treatment arms:

- LUM 400 mg/IVA 250 mg q12h for 24 weeks
- Placebo q12h for 24 weeks

2.1.2. Clinical study

Study VX15-809-112 (Study 112)

Title: A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-design Study of the Effect of Lumacaftor/Ivacaftor Combination Therapy on Exercise Tolerance in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Objectives

Primary objective:

The primary objective was to evaluate the effect of LUM/IVA on exercise tolerance in subjects with CF, homozygous for the F508del-CFTR mutation.

Secondary objective:

The secondary objective was to evaluate the effect of LUM/IVA on manifestations of CF affected by exercise tolerance and training.

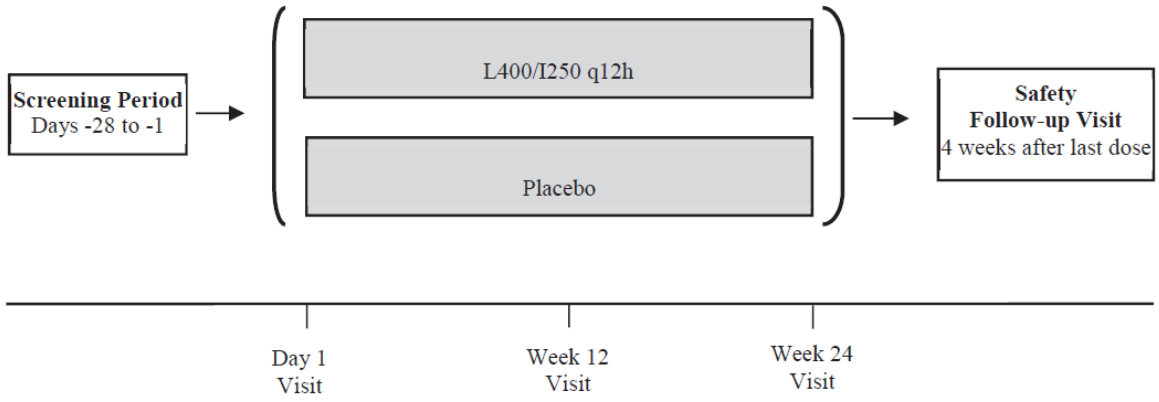
Study design

Study 112 was a randomised, double-blind, placebo-controlled, parallel-group, Phase IV study in CF subjects aged 12 years and older, homozygous for F508del. Subjects were randomised 1:1 to the treatment arms and stratified by percent predicted forced expiratory volume in 1 second (ppFEV1) at baseline (<70% and ≥70% predicted). Subjects received study drug (LUM/IVA or placebo) for a 24-week treatment period in addition to their current CF medication regimen.

This study was designed to evaluate the effect of LUM/IVA on exercise tolerance. Subjects were reminded of the standard exercise recommendations for CF patients; their daily activity was tracked using an actigraphy device.

A body composition substudy and a glucose tolerance substudy were conducted at selected sites.

Schematic of study design:



CHMP comment

The overall study design is considered acceptable. The study was conducted over 24 weeks and was placebo controlled throughout. Patients were encouraged to exercise in line with standard recommendations for CF patients. Actigraphy was used to capture continuous activity level data.

Study population

Principal inclusion criteria

- Sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis, as documented in either of the following:
  - i. subject's medical records
  - ii. sweat chloride test result obtained during screening (to be conducted only if the subject did not have a sweat chloride test result in the medical records)
- Homozygous for the *F508del-CFTR* mutation
- 12 years of age or older
- FEV_1 at least 40% and not greater than 90% of predicted at the Screening Visit

Principal exclusion criteria

- Subjects with a history of any comorbidity reviewed at the Screening Visit that could confound the results of the study, interfere with the use of CPET as an assessment, or pose an additional risk in administering study drug to the subject
- Any previous exposure to LUM or IVA
- Colonization with organisms associated with a more rapid decline in pulmonary status
- Subjects with protocol-defined laboratory values indicative of abnormal liver function or abnormal renal function

CHMP's comment

The subjects are Orkambi naïve. The threshold for sweat chloride specified as an inclusion criterion is more conservative than recently issued (2017) consensus recommendations (≥30 mmol/L).

The study was initiated before extension of the indication to patients 6 years and older homozygous for *F508del-CFTR*

The inclusion and exclusion criteria are considered appropriate.

Efficacy assessments

Efficacy assessments were conducted at the Week 12 and Week 24 visit and included:

Cardiopulmonary Exercise Testing (CPET)

Maximal cardiopulmonary testing was conducted using a cycle that ramps resistance over time, according to the modified Godfrey protocol. Data on a range of measures of gas exchange were collected including oxygen consumption (VO_2), functional VO_2 gain, carbon dioxide production (VCO_2), anerobic threshold (AT) and pulmonary ventilation (VT),

CHMP's comment

The measures are reflective of cardiopulmonary reserve, ventilatory efficiency and exercise intensity.

Spirometry

Spirometry was conducted post-bronchodilator and before study drug administration and CPET. Spirometry included FEV1, FVC, and FEF (forced expiratory flow in mid-expiration).

Actigraphy

Subjects were provided with a non-invasive, wrist-worn actigraphy device to be worn on their non-dominant hand 24 hours a day. The device continuously collected data on daily activity levels and sleep duration and quality. Actigraphy data were centrally read.

Patient questionnaires relating to depression and anxiety – PHQ-8 and GAD-7

Questionnaires (not specific to CF) relating to depression and anxiety were used given high rates of these symptoms in CF patients

Dual energy X-ray absorptiometry (DEXA)

DEXA scans were used in a body composition substudy to measure bone mineral density.

Glucose tolerance substudy

An oral glucose tolerance test (OGTT) and HBA1c measurement was used at screening and for monitoring of glucose tolerance in case of change due to altered exercise tolerance, conducted in a substudy.

Primary efficacy variable

Relative change in VO_{2max} during CPET at Week 24

CHMP's comment

The pre-specified primary endpoint was between group (active versus placebo) difference in change from baseline VO_{2max} (mL/kg/min) during CPET at 24 weeks.

VO_{2max} reflects maximum oxygen consumption during maximal exercise testing.

An increase in VO_{2max} reflects improvement in exercise tolerance.

Secondary efficacy variables

Key secondary efficacy variable:

- Relative Change From Baseline in Exercise Duration During CPET at Week 24

Additional secondary efficacy variables:

- Absolute Change From Baseline in Exercise Duration During CPET at Week 24
- Absolute Change From Baseline in VO_{2max} During CPET at Week 24
- Change From Baseline in VO_2 at AT at Week 24
- Change From Baseline in Functional VO2 Gain at Week 24
- Change From Baseline in VE Versus VCO2 Slope at Week 24
- Change From Baseline in ppFEV1 at Week 24
- Change From Baseline in BMI at Week 24
- Change From Baseline in CFQ-R Respiratory Domain Score at Week 24
- Change From Baseline in Total Daily Physical Activity as Determined by Actigraphy at Week 24

Statistical Methods

The primary efficacy analysis was conducted using mixed effects model for repeated measures (MMRM). The model included percentage change from baseline in VO_{2max} as the dependent variable, subject as random effect and treatment, visit, treatment-by-visit interaction as fixed effects, with adjustment for gender, age and $ppFEV_1$ at baseline and VO2max at baseline.

The model was used to test the difference between LUM/IVA and placebo, and the primary result obtained from the model was the treatment effect at week 24.

With an MMRM based on an RML (restricted maximum likelihood) estimation and assuming that data were missing at random, no imputation of missing data was performed.

Results

Study population

66 subjects were planned to be randomised (33 per treatment group).

The final number of patients in each analysis set is provided below:

Analysis population (definition)	Placebo	L400/I250 q12h	Overall
All Subjects Set (randomized or dosed)	36	34	70
Full Analysis Set (randomized and dosed)	36	34	70
Safety Set (dosed)	36	34	70

Source: Table 14.1.1
q12h: every 12 hours

All 70 randomised subjects received at least one dose of study treatment and 67 (95.7%) subjects completed both study treatment and study. One subjects discontinued treatment due to study drug non-compliance and 2 subjects discontinued due to AEs: 1 with pulmonary exacerbation and 1 with multiple AEs, primarily in the SOC of GI disorders. No subjects were excluded from any analysis set.

Each substudy was planned to include approximately 5 to 10 subjects from the main study. The final number of subjects was 24 in the body composition study and 7 in the glucose tolerance.

All subjects were White. 55.7% were male and the median age was 25.0 years. The median BMI was 21.2 kg/m2.

CHMP's comment

Subject demographics were overall balanced between treatment arms. However, there were more males than females (61.8% versus 38.2%) in the active treatment arm whereas the genders were balanced in the placebo arm. Females tend to have a more severe disease course than males and the higher proportion of males in the LUM/IVA arm could have benefited overall exercise tolerance in the active treatment arm.

Median BMI was in the normal range. However, the baseline median BMI z-score was less than zero (-0.03) in the age group under 20 years suggesting the younger patients were under-nourished. BMI was balanced between treatment arms at all ages.

Median ppFEV1 at baseline was 64.1 and 64.5 in the respective treatment arms.

The common medical history conditions and prior and concomitant medications used were consistent with those of a CF population.

Efficacy results

Primary analysis

MMRM analysis of relative change from baseline in VO_{2max} (ml/kg/min) during CPET through Week 24, FAS

Statistic	Placebo N = 36	L400/I250 q12h N = 34
Baseline		
n	35	32
Mean (SD)	32.1 (7.52)	31.8 (8.80)
Relative change at Week 24 (%)		
n	32	26
Mean (SD)	-3.5 (10.49)	-7.2 (13.23)
LS mean (SE)	-3.5 (2.12)	-6.6 (2.33)
95% CI of LS mean	(-7.7, 0.8)	(-11.3, -2.0)
P value within treatment	0.1073	0.0061
LS mean difference (SE)	NA	-3.2 (3.03)
95% CI of LS mean difference	NA	(-9.2, 2.9)
P value versus placebo	NA	0.3021
***P* value for treatment by visit**	0.0982	

Source: Table 14.2.1.2

CPET: cardiopulmonary exercise test; DOF: degrees of freedom; FAS: Full Analysis Set; LS: least squares; MMRM: mixed-effects model for repeated measures; N: total sample size; n: size of subsample; NA: not applicable; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; VO_{2max}: maximal oxygen consumption

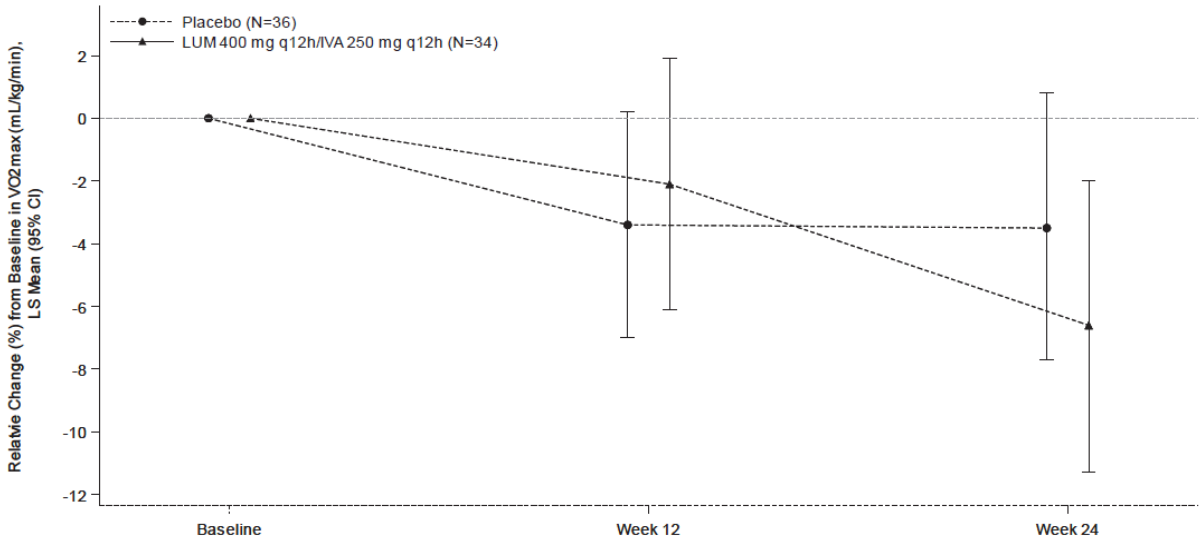
Notes: *P* values are from an MMRM that included treatment, visit, and treatment-by-visit interaction as fixed effects and subject as a random effect, with adjustments for sex, baseline age group (<18 or ≥18 years of age), baseline ppFEV1 (<70 or ≥70), and baseline VO2max. The analysis included all measurements up to Week 24, whether on treatment or after treatment discontinuation. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator DOF.

CHMP's comment

The primary endpoint was the between group treatment difference in change from baseline VO_{2max} through to week 24 . The LS mean treatment difference (95% CI) between active and placebo was -3.2 (-9.2, 2.9). In both treatment arms there was a worsening of exercise tolerance from baseline which was more apparent in the LUM/IVA arm (LS mean -6.6 vs -3.5, LUM/IVA vs placebo) and the entire CI for mean change from baseline was below zero for the within LUM/IVA -treatment group (95% CI of LS mean -11.3, -2.0, p=0.0061).

The primary endpoint for the treatment difference was not met (p=0.3021).

Relative change from baseline in VO_{2max} (ml/kg/min) during CPET at each visit, FAS



Source: Figure 14.2.1.1

CPET: cardiopulmonary exercise test; DOF: degrees of freedom; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; MMRM: mixed-effects model for repeated measures; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; VO_{2max}: maximal oxygen consumption

Notes: LS means and 95% CIs are from an MMRM that included treatment, visit, and treatment-by-visit interaction as fixed effects and subject as a random effect, with adjustments for sex, baseline age group (<18 or ≥18 years of age), baseline $ppFEV_1$ (<70 or ≥70), and baseline VO_{2max}. The analysis included all measurements up to Week 24, whether on treatment or after treatment discontinuation. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator DOF.

CHMP's comment

Three sensitivity analyses (MMRM analysis that included only on-treatment measurements; rank of relative change in VO2max during CPET from baseline at week 2 analysed using ANCOVA; MMRM analysis of VO2max in ml/min) all demonstrated a consistent trend in favour of placebo i.e. more evident deterioration in exercise tolerance with LUM/IVA.

Pre-specified subgroup analyses

Subgroups by age

Subgroup MMRM analyses of relative change from baseline in VO_{2max} (ml/kg/min) during CPET at week 24, FAS

Subgroup Relative Change at Week 24, Statistic	Placebo N = 36	L400/I250 q12h N = 34
Subgroups by age		
≥12 to <18 years of age[a]		
n	9	8
Baseline mean (SD)	32.3 (6.25)	39.2 (10.84)
Mean (SD)	0.0 (9.67)	-11.2 (13.56)
LS mean (SE)	-1.0 (3.43)	-6.0 (4.20)
95% CI of LS mean	(-8.4, 6.4)	(-15.1, 3.1)
P value within treatment	0.7706	0.1767
LS mean difference (SE)	NA	-5.0 (5.18)
95% CI of LS mean difference	NA	(-16.2, 6.2)
P value versus placebo	NA	0.3534
≥18 years of age[a]		
n	23	18
Baseline mean (SD)	31.7 (8.40)	30.8 (6.56)
Mean (SD)	-4.8 (10.68)	-5.4 (13.07)
LS mean (SE)	-4.5 (2.58)	-4.7 (2.94)
95% CI of LS mean	(-9.7, 0.7)	(-10.6, 1.2)
P value within treatment	0.0912	0.1163
LS mean difference (SE)	NA	-0.2 (3.83)
95% CI of LS mean difference	NA	(-8.0, 7.5)
P value versus placebo	NA	0.9488

CHMP's comment

The deterioration in exercise tolerance was demonstrated in both treatment arms and both age groups although the treatment difference was greater in the under 18 years age group (LUM/IVA vs placebo, LS mean; 95% CI: -5.0; -16.2, 6.2 versus -0.2; -8.0, 7.5). The MAH asserts that the greater treatment difference in younger patients (LS mean difference -5.0 versus -0.2) is due to the challenge of conducting CPET in this age group, leading to greater variability. It is acknowledged that maximal exercise testing - as performed – will require greater cooperation and motivation that could be more challenging with younger patients. However, the same challenge will be faced in both treatment arms and the confidence intervals are wide in both age groups. Moreover, the subgroup analysis is consistent with the primary analysis, and the sensitivity analyses, which demonstrate a consistent trend to greater deterioration in maximal oxygen consumption (exercise tolerance under maximal testing conditions) from baseline in LUM/IVA treated subjects compared with placebo treated subjects. This is also despite the higher proportion of males in the LUM/IVA arm which could have benefited exercise tolerance outcomes on active treatment given that females tend to have a worse disease course.

The results of the primary analysis are therefore of concern as the data do not support meaningful benefit on cardiopulmonary function after 6 months of treatment despite the previous pivotal study evidence of improvement in ppFEV1 with Orkambi. It is acknowledged that the data are not conclusive given the small size of the study and the challenges of conducting exercise testing under maximal

conditions in the paediatric population. It may also be challenging to demonstrate meaningful improvement in cardiorespiratory function, sufficient to reveal difference in maximal exercise tolerance, in patients with the most severe manifestation of CF at a 6 month time point. Nonetheless, further clarification is required including consideration of how more definitive data may be obtained.

The MAH is requested to provide additional randomised controlled trial data, if available, from alternative measures of exercise tolerance such as the 6MWT (6 minute walk test) or modified shuttle walk test, or using alternative measures of exercise tolerance that do not require maximum effort.

In addition, given that CF guidelines recommend that exercise tolerance, using CPET or the like, is monitored on an annual basis in CF patients, CF registry data relevant to exercise tolerance in *F508del* homozygous patients treated with Orkambi compared with *F508del* homozygous patients receiving standard of care is also sought. The MAH is furthermore requested to discuss more generally how exercise tolerance is being captured in the ongoing registry studies, and whether this could be intensified in view of the inconclusive data from this study.

Key Secondary Endpoint

Exercise Duration During CPET

The key secondary endpoint was not met. The LS mean treatment difference in the relative change in exercise duration during CPET from baseline at Week 24 was -3.2 percentage points (P = 0.1894); the within-group LS mean change in exercise duration was -2.8% in the LUM/IVA group and 0.4% in the placebo group. Results were similar in the analysis based on the absolute change from baseline.

CHMP's comment

The key secondary endpoint was not met and was consistent with the primary analysis in suggesting a greater deterioration in exercise tolerance from baseline in the LUM/IVA treated patients.

Additional Secondary Endpoints

Exercise tolerance endpoints

Additional secondary endpoints related to exercise tolerance were not met. These endpoints were evaluated using CPET and included absolute changes from baseline in oxygen consumption (VO2) at anaerobic threshold (AT), in VO2 functional gain, and in the pulmonary ventilation (VE) versus carbon dioxide production (VCO2) slope.

VO_2 at AT

At Week 24, the LS mean treatment difference in the absolute change from baseline in VO2 at AT was -149.6 mL/min (P = 0.0439). The within-group LS mean change in VO2 at AT was -55.1 mL/min in the LUM/IVA group and 94.6 mL/min in the placebo group.

Functional VO_2 Gain

At Week 24, the LS mean treatment difference in the absolute change from baseline in functional VO2 gain was -0.60 mL/min/watt (P = 0.0226). The within-group LS mean change in functional VO2 gain was -0.53 mL/min/watt in the LUM/IVA group and 0.07 mL/min/watt in the placebo group.

VE Versus VCO_2:

At Week 24, the LS mean treatment difference in the absolute change from baseline in VE versus VCO2 slope was 0.3. The within-group LS mean change in VE versus VCO2 slope was 0.8 in the LUM/IVA group and 0.5 in the placebo group.

CHMP's comment

Additional secondary endpoints reflective of exercise tolerance were not met and were consistent with the primary analysis in suggesting a trend in favour of placebo i.e. greater worsening of exercise tolerance in patients treated with LUM/IVA compared to placebo.

There is nothing in the baseline data to suggest that the analysis has been biased in favour of placebo and if anything, the gender imbalance would have favoured active treatment.

Conventional CF endpoints

Secondary endpoints related to standard assessments of CF were also evaluated. These included absolute changes from baseline in ppFEV1, body mass index (BMI), and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score (pooled).

Spirometry:

The LS mean treatment difference in the absolute change in ppFEV1 from baseline at Week 24 was 3.4 percentage points (P = 0.1460); the within-group LS mean change in ppFEV1 was -0.6 percentage points in the LUM/IVA group (P = 0.7438) and -4.0 percentage points in the placebo group (P = 0.0189).

MMRM analysis of absolute change from baseline in ppFEV1 at Week 24

Statistic	Placebo N = 36	L400/I250 q12h N = 34
Baseline		
n	36	34
Mean (SD)	67.5 (19.33)	65.6 (15.00)
Absolute change at Week 24		
n	32	30
Mean (SD)	-4.6 (8.93)	-0.5 (9.43)
LS mean (SE)	-4.0 (1.65)	-0.6 (1.71)
95% CI of LS mean	(-7.3, -0.7)	(-4.0, 2.9)
P value within treatment	0.0189	0.7438
LS mean difference (SE)	NA	3.4 (2.33)
95% CI of LS mean difference	NA	(-1.2, 8.1)
P value versus placebo	NA	0.1460
***P* value for treatment by visit**	0.9391	

Source: Table 14.2.2.6.2

DOF: degrees of freedom; FAS: Full Analysis Set; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; NA: not applicable; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours

Notes: *P* values are from an MMRM that included treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustments for sex, baseline age group (<18 or ≥18 years of age), and baseline $ppFEV_1$ (<70 or ≥70). The analysis included all measurements up to Week 24, whether on treatment or after treatment discontinuation. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator DOF.

CHMP's comment

The results for ppFEV1 were inconsistent with the exercise tolerance outcomes in demonstrating a greater decline from baseline in ppFEV1 in the placebo treated arm (LS mean -4.0, 95% CI -7.3, -0.7) compared with the LUM/IVA arm (LS mean -0.6, 95% CI -4.0, 2.9) suggesting a more favourable outcome on respiratory function in LUM/IVA treated patients. However, improvement in ppFEV1 might have been expected from the pivotal registration studies and this was not demonstrated. The MAH attributes this to non-standard procedures for spirometric assessment which is difficult to understand when specialist centres were involved in the study. A discrepancy between ppFEV1 and exercise tolerance has been reported by previous investigators and questions the robustness of spirometric outcomes for pivotal efficacy assessment although exercise tolerance may also present challenges to interpretation. Discussion of the discrepancy between spirometry and exercise tolerance is invited.

BMI:

The LS mean treatment difference in the absolute change in BMI from baseline at Week 24 was 0.2 kg/m2 (P = 0.3961); the within-group LS mean change in BMI was 0.5 kg/m2 in the LUM/IVA group (P = 0.0054) and 0.3 kg/m2 in the placebo group (P = 0.0760)

CFQ-R

The LS mean treatment difference in the absolute change in CFQ-R respiratory domain score from baseline at Week 24 was 6.2 (P = 0.1257); the within-group LS mean change in CFQ-R respiratory domain score was 0.1 in the LUM/IVA group and -6.1 in the placebo group.

CHMP's comment

BMI and CFQ-R did not reveal any meaningful treatment difference

Depression and anxiety endpoints

Several recent studies have documented the high rates of symptoms of depression and anxiety in patients with CF.

PHQ-8 and GAD-7

No clinically meaningful trends between groups or within-group were observed in the endpoints of Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder (GAD-7).

Actigraphy-based endpoints

Exercise tolerance can be affected by a number of factors, including activity level. Activity levels were thus monitored using actigraphy, along with sleep/wake data that could reflect both functional and physiological health of subjects.

Total Daily Physical Activity, Sleep Time During the Night, and Time Above Sedentary Duration

No clinically meaningful trends were observed between groups or within-group in the endpoints of physical activity, sleep duration, or time above sedentary duration.

Correlation analyses

No clinically meaningful correlations were observed between the CPET endpoints compared with the conventional CF endpoint of ppFEV1 (VX15-809-112 CSR/Section 11.2.1.3.13).

Sub-studies

Twenty-four subjects (9 in the placebo group and 15 in the LUM/IVA group) participated in the body composition substudy, which evaluated changes in body composition and bone mineral density by DEXA. Exercise training has been shown to increase bone mineral density and change body composition.

Seven subjects participated in the glucose tolerance substudy, which evaluated changes in blood glucose levels during OGTT. The OGTT is the most sensitive and the recommended screening tool for CF-related diabetes.

No clinically meaningful trends between groups or within-group were observed in the body composition and glucose tolerance substudies, each of which had limited population sizes.

Discussion on efficacy

Study 112 was a small study conducted in 70 patients over 24 weeks, designed to investigate exercise tolerance in CF patients aged 12 years and above, homozygous for *F508 del*, randomised to receive either Orkambi or placebo.

Efficacy assessments were conducted at Week 12 and Week 24. The primary efficacy variable was change from baseline in maximal oxygen consumption VO_{2max}, measured during cardiopulmonary exercise testing using a ramped cycle ergometer requiring maximum effort. The primary endpoint evaluated the between group treatment difference (LUM/IVA versus placebo) analysed using MMRM through to Week 24.

A range of additional secondary endpoints that evaluated exercise tolerance including gas exchange and exercise duration were evaluated.

Conventional CF endpoints (ppFEV1 by spirometry, BMI and CFQ-R) were also evaluated as well as depression and anxiety endpoints.

Activity levels were assessed by continuous actigraphy.

Substudies of bone mineral density and glucose tolerance were also conducted.

Results

The primary endpoint for the treatment difference in change baseline VO_{2max} through to week 24 was not met (p=0.3021). The LS mean treatment difference (95% CI) between active and placebo was -3.2 (-9.2, 2.9). In both treatment arms there was a worsening of exercise tolerance from baseline which was more apparent in the LUM/IVA arm (LS mean -6.6 vs -3.5, LUM/IVA vs placebo) and the entire CI for mean change from baseline was below zero for the within LUM/IVA -treatment group (95% CI of LS mean -11.3, -2.0, p=0.0061).

Sensitivity analyses also demonstrated a trend in favour of placebo.

Subgroup analysis by age (≥12 yrs to < 18 yrs and ≥ 18 yrs) demonstrated deterioration in exercise tolerance in both treatment arms and both age groups although the treatment difference was greater in the under 18 years age group (LUM/IVA vs placebo, LS mean; 95% CI: -5.0; -16.2, 6.2 versus -0.2; -8.0, 7.5).

The MAH asserts that the greater treatment difference in younger patients (LS mean difference -5.0 versus -0.2) is due to the challenge of conducting CPET in this age group, leading to greater variability. It is acknowledged that maximal exercise testing - as performed – will require greater cooperation and motivation that could be more challenging with younger patients. However, the same challenge will be faced in both treatment arms and the confidence intervals are wide in both age groups. Moreover, the

subgroup analysis is consistent with the primary analysis, and the sensitivity analyses, which demonstrate a consistent trend to greater deterioration in maximal oxygen consumption (exercise tolerance under maximal testing conditions) from baseline in LUM/IVA treated subjects compared with placebo treated subjects. This is also despite the higher proportion of males in the LUM/IVA arm which could have benefited exercise tolerance outcomes on active treatment given that females tend to have a worse disease course.

The results of the primary analysis are therefore of concern as the data do not support meaningful benefit on cardiopulmonary function after 6 months of treatment despite the previous pivotal study evidence of improvement in ppFEV1 with Orkambi. It is acknowledged that the data are not conclusive given the small size of the study and the challenges of conducting exercise testing under maximal conditions in the paediatric population. It may also be challenging to demonstrate meaningful improvement in cardiorespiratory function, sufficient to reveal difference in maximal exercise tolerance, in patients with the most severe manifestation of CF at a 6 month time point. Nonetheless, further clarification is required including consideration of how more definitive data may be obtained.

The secondary endpoints do not provide reassurance. None of the secondary endpoints reflective of exercise tolerance were met, and as with the primary efficacy analysis, there was a trend in favour of placebo i.e. greater worsening of exercise tolerance in patients treated with LUM/IVA compared to placebo.

The results for ppFEV1 were inconsistent with the exercise tolerance outcomes in demonstrating a greater decline from baseline in ppFEV1 in the placebo treated arm (LS mean -4.0, 95% CI -7.3, -0.7) compared with the LUM/IVA arm (LS mean -0.6, 95% CI -4.0, 2.9) suggesting a more favourable outcome on respiratory function in LUM/IVA treated patients. However, improvement in ppFEV1 might have been expected from the pivotal registration studies and this was not demonstrated. The MAH attributes this to non-standard procedures for spirometric assessment which is difficult to understand when specialist centres were involved in the study. A discrepancy between ppFEV1 and exercise tolerance has been reported by previous investigators and questions the robustness of spirometric outcomes for pivotal efficacy assessment although exercise tolerance may also present challenges to interpretation. Discussion of the discrepancy between spirometry and exercise tolerance is invited.

BMI and CFQ-R, or depression and anxiety scores, did not reveal any meaningful treatment difference.

No clinically meaningful trends in activity levels were observed from actigraphy.

No clinically meaningful trends between groups or within-group were observed in the body composition and glucose tolerance substudies, although very small numbers of patients were studied (24 and 7 respectively).

Safety

Administration of LUM 400 mg/IVA 250 mg q12h for approximately 24 weeks was generally safe and well tolerated in subjects aged 12 years and older with CF. The majority of subjects had AEs that were considered mild or moderate in severity; there were no deaths or life-threatening AEs. The most common serious adverse event (≥10% in any treatment group) was infective PEx of CF, which is a typical background event in subjects with CF. The most common AEs (≥15% in any treatment group) were infective PEx of CF, respiration abnormal, and cough. Two (5.9%) subjects in the LUM/IVA group had AEs that led to treatment discontinuation: 1 subject had an infective PEx of CF, and 1 subject had several AEs, primarily gastrointestinal in nature. One subject in the LUM/IVA group had AEs that led to study drug interruption. No subjects had treatment discontinuations or interruptions in the placebo group. No important trends attributable to LUM/IVA were identified from chemistry, hematology, urinalysis, pulse oximetry, vital signs, or ophthalmologic examinations. No subjects in the LUM/IVA

group had elevations above the predefined thresholds in alanine transaminase, aspartate transaminase, alkaline phosphatase, or total bilirubin.

Overall, the safety results were generally consistent with the known safety profile of LUM/IVA; no new safety concerns were identified.

3. Rapporteur's Overall Conclusion and Recommendation

A deterioration in exercise tolerance was observed in both Orkambi and placebo treated patients over a 24 week period. Although the results can be considered inconclusive due in part due to the small size of the study and the challenges posed by exercise testing requiring maximum effort in a paediatric population, there is concern over a trend to consistently greater deterioration from baseline in exercise tolerance outcomes in the Orkambi arm compared to the placebo arm. There is nothing in the baseline data to suggest bias in favour of placebo and if anything, a gender imbalance could have biased in favour of active treatment. A number of clarifications are therefore sought and in particular, consideration of how more definitive data may be obtained.

4. Clarifications requested

1. The MAH is requested to provide additional randomised controlled trial data, if available, from alternative measures of exercise tolerance such as the 6MWT (6 minute walk test) or modified shuttle walk test, or using alternative measures of exercise tolerance that do not require maximum effort.
2. Given that CF guidelines recommend that exercise tolerance, using CPET or similar, is monitored on an annual basis in CF patients, CF registry data relevant to exercise tolerance in *F508del* homozygous patients treated with Orkambi compared with *F508del* homozygous patients receiving standard of care is sought. The MAH is furthermore requested to discuss more generally how exercise tolerance is being captured in the ongoing CF registry studies, and whether this could be intensified in view of the inconclusive data from this study.
3. Discussion of the discrepancy between spirometry and exercise tolerance is sought.
4. Discussion of the discrepancy between lack of improvement in ppFEV1 with Orkambi in the Phase IV study, compared with the improvement in spirometry demonstrated in the pivotal registration studies for Orkambi, is also sought. A comparison with spirometric data obtained with Orkambi from registry data, is also sought. Similar to the Phase IV study, registry data will have been collected under real world conditions.

5. Assessment of responses to the points for clarification

Question 1

The MAH is requested to provide additional randomised controlled trial data, if available, from alternative measures of exercise tolerance such as the 6MWT (6 minute walk test) or modified shuttle walk test, or using alternative measures of exercise tolerance that do not require maximum effort.

MAH response

No additional data are available from Vertex-sponsored, randomized, placebo-controlled trials of the effect of LUM/IVA on maximal or submaximal exercise tolerance. After searching the literature, Vertex has not found any additional published, randomized, placebo-controlled trials of LUM/IVA's effects on

exercise tolerance, including alternative measures of tolerance, such as the 6-minute walk test or the shuttle walk test.

Assessment of response and conclusion

No additional RCT data are available.

Point unresolved.

Question 2

Given that CF guidelines recommend that exercise tolerance, using CPET or similar, is monitored on an annual basis in CF patients, CF registry data relevant to exercise tolerance in F508del homozygous patients treated with Orkambi compared with F508del homozygous patients receiving standard of care is sought. The MAH is furthermore requested to discuss more generally how exercise tolerance is being captured in the ongoing CF registry studies, and whether this could be intensified in view of the inconclusive data from this study.

MAH response

It is Vertex's understanding that the data captured in the CF patient registries are limited to tests that are performed routinely in CF clinics (decisions regarding registry data collection are made by the registry governing bodies). Although annual exercise tolerance testing is recommended for patients with CF, it is our understanding that this is not routinely implemented in CF clinics in the US, EU, or Australia at present. Consequently, based on evaluation of the data collection forms and/or published data reports from the US, European, and Australian CF registries, data on exercise tolerance are either not collected by the registries, or data are very limited and insufficient for robust evaluation of this endpoint.

Vertex, as a manufacturer, cannot influence clinics' adherence to the recommendation to perform exercise testing. We do not believe that the outcome of this small, exploratory study would merit registry-wide efforts to intensify collection of exercise tolerance data.

Assessment of response and conclusion

The MAH asserts that in routine clinical practice, exercise tolerance is not monitored and therefore CF registry data are not available.

Point unresolved.

Question 3

Discussion of the discrepancy between spirometry and exercise tolerance is sought.

MAH response

Given the limitations of the spirometry and exercise tolerance data in this small exploratory study, it is not possible to draw meaningful conclusions about the potential discrepancy between these endpoints.

Assessment of response and conclusion

No discussion has been provided.

Point unresolved.

Question 4

Discussion of the discrepancy between lack of improvement in ppFEV1 with Orkambi in the Phase IV study, compared with the improvement in spirometry demonstrated in the pivotal registration studies for Orkambi, is also sought. A comparison with spirometric data obtained with Orkambi from registry data, is also sought. Similar to the Phase IV study, registry data will have been collected under real world conditions.

MAH response

Comparison to Phase 3 Studies

The pivotal Phase 3 studies (Study 103 and 104) were powered for ppFEV1 and demonstrated a statistically significant benefit of LUM/IVA on multiple clinical endpoints, including ppFEV1. In contrast, evaluation of ppFEV1 was not the primary objective of Study 112; the study was not powered to detect a treatment effect in this endpoint. The expected effect on lung function was not observed, which limits the ability to draw any conclusions from this study. As described above, differences in the spirometry equipment used in Study 112 compared to the pivotal Phase 3 studies may also have impacted the variability of the spirometry results, further limiting the ability to interpret these data.

Comparison to Real-World Registry Data

Limited real-world spirometry data are available at this time. Data from the CFF patient registry were evaluated in the first annual interim analysis report of the LUM/IVA Post-Authorization Safety Study (PASS). This registry study was not designed to evaluate short-term improvements in spirometry and focused instead on evaluation of long-term patterns. Furthermore, the first interim report was limited by the fact that many subjects were treated with LUM/IVA for less than a year at the time of data analysis.

Despite this limitation, the results of this report were favourable with respect to clinically important outcomes in LUM/IVA-treated patients. Patients who were treated with LUM/IVA (N = 5,508) demonstrated numerically lower lung function (ppFEV1) decline from pre-treatment baseline year (2014) through 2016, as compared to the comparator cohort of F508del heterozygous patients with a similar baseline disease state who had never received marketed LUM/IVA or IVA monotherapy (N = 3,990). No new safety concerns were identified. These findings are consistent with the current understanding of LUM/IVA's safety profile and clinical benefits.

Conclusion

The Phase 3 pivotal data provide robust evidence of LUM/IVA's safety and efficacy. Ongoing clinical experience continues to support a positive benefit-risk profile for LUM/IVA. Study 112 was a small, exploratory study that cannot be used to draw meaningful conclusions about efficacy.

Assessment of response and conclusion

Although study 112 did not replicate the improvement in ppFEV1 demonstrated in the pivotal 103/104 studies of LUM/IVA in homozygous F508del patients, there was a lesser decline from baseline in mean ppFEV1 in patients receiving LUM/IVA, compared with those receiving placebo. This is consistent with the first annual interim analysis report from the PASS of LUM/IVA treated F508del homozygous patients compared to a cohort of untreated patients where a lessening of decline but no improvement in ppFEV1 was observed in LUM/IVA treated patients. A lessening of decline in ppFEV1 is therefore likely to represent the efficacy benefit in the real world.

Point resolved.

6. Rapporteur's Overall Conclusion and Recommendation following the Assessment of MAH responses

Three of the above clarification points remain unresolved.

Study VX15-809-112 (Study 112) was submitted as a stand-alone post-authorisation measure under Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation'). The intention of Study 112was to obtain data based on exercise tolerance to support clinical relevance of the benefit on pulmonary function with Orkambi in F508del patients from the age of 12 years, that had been demonstrated in the pivotal registration studies.

Study 112 demonstrates a concerning trend to consistently greater deterioration from baseline in exercise tolerance outcomes in the LUM/IVA arm compared to the placebo arm. The MAH asserts in the responses that no conclusions can be drawn from the data given that study 112 was small and exploratory in nature and that RCT or registry data on exercise tolerance in CF patients are not available to help address the concern in relation to the trend to worse exercise performance with LUM/IVA.

There is also concern at the inconsistency between the exercise tolerance outcomes and change from baseline in ppFEV1 where there was a lesser deterioration from baseline with LUM/IVA compared to placebo, in contrast to the exercise tolerance endpoints.

A further discrepancy was noted in the failure of study 112 to replicate improvement in ppFEV1, that had previously been demonstrated in the pivotal studies 103 and 104. The MAH reports that this is consistent with the first annual interim analysis from the PASS of LUM/IVA treated F508del homozygous patients compared to a cohort of untreated patients where a lessening of decline but no improvement in ppFEV1 was observed in LUM/IVA treated patients. A lessening of decline in ppFEV1 is therefore likely to represent the efficacy benefit in the real world. This point is considered resolved.

However, the points in relation to exercise tolerance have not been adequately addressed. It is not sufficient for the MAH to dismiss study 112 as being exploratory without proposing an alternative way in which to address the objective of the PAM. It is acknowledged that the study may have been inadequately powered to demonstrate a treatment difference for LUM/IVA from placebo. However, at least a trend to benefit could have been reasonably expected, particularly given the trend to benefit in respiratory function, albeit not of the same order as that in the pivotal registration studies. Instead, the results from study 112 suggest a consistent trend to worsening of exercise tolerance in Orkambi treated patients, compared to placebo, which was not expected.

The MAH dismisses the study 112 results as inconclusive due to the small size and exploratory nature of the study. However, this precludes adequate discussion around the clinical implications of any effects of LUM/IVA on exercise performance, be these favourable or unfavourable, in the context of overall benefit-risk for the product. A more reliable dataset would therefore be required to inform this discussion, in which regard the MAH may wish to consider conducting a further Phase IV study to investigate maximal and submaximal exercise tolerance in F508del homozygous CF patients from the age of 12 years.

In conclusion, as requested by the legal requirements of Art. 46 of Regulation (EC) No 1901/2006, the results of Study 112 were submitted to EMA within six months of study completion.

The MAH asserts that additional RCT data, or registry data, on exercise tolerance in CF patients are not available. These were sought as potential alternative ways of satisfying the PAM. In the absence of alternative sources of information, study 112, submitted as a stand-

alone post-authorisation measure, is considered to have failed in its objective to evaluate the effect of LUM/IVA on exercise tolerance in patients with cystic fibrosis, homozygous for the *F508del-CFTR* mutation.

7. Outstanding issues

Not applicable