EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/PRAC/594359/2018
Human Medicines Evaluation Division

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

Orkambi

lumacaftor / ivacaftor

Procedure no: EMEA/H/C/003954/P46/011

Note

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

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 011

Marketing authorisation holder: Vertex Pharmaceuticals (Europe) Limited

Rapporteur:	UK
Start of the procedure:	02/04/2018
Date of this report:	24/05/2018
Deadline for CHMP member's comments:	NA
Date of the Rapporteur's final report:	24/05/2018
CHMP Conclusion	31/05/2018

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Administrative information

Rapporteur's contact person:	**Name: Nithyanandan Nagercoil** Tel: 020 3080 6379 Email: Nithyanandan.Nagercoil@mhra.gov.uk
Name of the Assessor:	**Name: Ayesha De Costa** Tel: 020 3080 7057 Email: Ayesha.decosta@mhra.gov.uk
Procedure Manager:	**Name: Elisa Pedone** Fax: +44 20 7418 8545 Email: elisa.pedone@emea.europa.eu

Table of contents

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 stated that study titled 'A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, and Being Treated With Orkambi' (study no: VX15-371-101) is a stand-alone study.

The abbreviated CSR for Study VX15-371-101 is being submitted under Article 46 of Regulation because it involved the use of the authorized medicinal product Orkambi™ as a standard of care treatment for all subjects (including pediatric subjects aged ≥ 12 to <18 years) participating in the study.

The efficacy of Orkambi was not evaluated as part of this study.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted an abbreviated clinical study report for:

•'A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, and Being Treated With Orkambi' (study no: VX15-371-101)

2.2.2. Clinical study

'A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, and Being Treated With Orkambi' (study no: VX15-371-101)

Description

Study VX15-371-101 is being submitted under Article 46 of Regulation (EC) No 1901/2006 because it involved the use of the authorized medicinal product Orkambi™ as a standard of care treatment for all subjects (including pediatric subjects aged ≥ 12 to <18 years) participating in the study.

Study VX15-371-101 was a Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter study in subjects ≥ 12 years of age with cystic fibrosis (CF) who were F508del homozygous and treated with Orkambi (2 tablets LUM 200 mg/IVA 125 mg administered orally every 12 hours). All subjects were to receive stable Orkambi treatment for at least 28 days before the first dose of inhaled study drug (VX-371 + hypertonic saline (4.2% saline) [HS], HS, VX-371 + placebo (1.7% saline), or placebo) and through the Safety Follow-up Telephone Contact or Safety Follow-up Visit, which was to occur 28 days after the last dose of study drug.

The efficacy of Orkambi was not evaluated as part of this study.

The primary objective was to evaluate the safety and efficacy of treatment with VX-371 in HS compared to HS alone in subjects with CF who are ≥ 12 years of age, homozygous for the F508del-CFTR
mutation, and being treated with Orkambi.

Rationale for this study:

Mucociliary clearance (MCC) is an important airway defense mechanism that is essential for respiratory health. The primary function of MCC is to clear inhaled particles, including inflammatory and infectious agents, from the surface of the lung. MCC depends on the coordinated, high frequency beating action of the cilia that cover the inner surface of the airways. Efficient ciliary motion is in turn dependent on proper regulation of hydration on the epithelial surface. Volume depletion of the airway surface liquid (ASL) compromises the efficiency of MCC.11 Inhaled therapies available to improve MCC include Pulmozyme (recombinant human dornase alfa, Roche/Genentech), which facilitates expectoration by breaking down DNA and decreasing sputum viscosity, and hypertonic saline (HS), which may improve airway surface hydration and improve MCC.

For reasons that are not fully understood, CF is also associated with a paradoxically increased activity of epithelial sodium channels (ENaC). The resulting combination of inadequate secretion of chloride ions and excessive intracellular transport of sodium ions creates an osmotic gradient that results in relative dehydration of the secretions in the airway lumen. Inadequate clearance of secretions predisposes the airways to bacterial infection.

When applied topically to the airway, ENaC inhibitors such as amiloride can decrease ENaC activity, increase ASL height, and increase MCC.14 While amiloride's low potency, hyperkalemia, and short half-life in the airway make it impractical as a clinical therapy, newer generations of inhaled ENaC inhibitors featuring an amiloride pharmacophore have been designed to potently inhibit ENaC function directly on the respiratory epithelium, while minimizing exposure to renal ENaC, thereby reducing the risk of hyperkalemia and increasing the therapeutic index.

VX-371 is a new chemical entity belonging to a family of amiloride derivatives referred to as pyrazinoylguanidines. VX-371 is a novel ENaC inhibitor that inhibits transport of sodium through direct exofacial block of the ENaC. It is hypothesized that the inhibition of ENaC activity with VX-371 will increase hydration of airway secretions rendering them more susceptible to MCC and cough clearance in subjects with CF.

Methods

Objective(s)

The primary objective was to evaluate the safety and efficacy of treatment with VX-371 in HS compared to HS alone in subjects with CF who are ≥ 12 years of age, homozygous for the F508del-CFTR
mutation, and being treated with Orkambi.

Secondary objectives included the following:

- To evaluate the efficacy of treatment with VX-371 in HS compared with placebo
- To evaluate the efficacy of treatment with VX-371 in HS compared with VX-371 in placebo
- To evaluate the efficacy of treatment with VX-371 in placebo compared with placebo
- To investigate the pharmacokinetics of VX-371

Study design

This was a Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter study in subjects ≥ 12 years of age with CF who were F508del homozygous and treated with
Orkambi. All subjects were to receive stable Orkambi treatment starting before the first dose of inhaled study drug and through the Safety Follow-up Telephone Contact or Safety Follow-up Visit.

Approximately 150 subjects were planned to be randomized to 1 of the 4 treatment sequences as described in Table 9-1. Each treatment sequence included the following study periods: Treatment Period 1, Washout, and Treatment Period 2.

Table 9-1 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2	Number of Planned Subjects
1	VX-371 + HS	HS	50
2	HS	VX-371 + HS	50
3	VX-371 + Placebo	Placebo	25
4	Placebo	VX-371 + Placebo	25

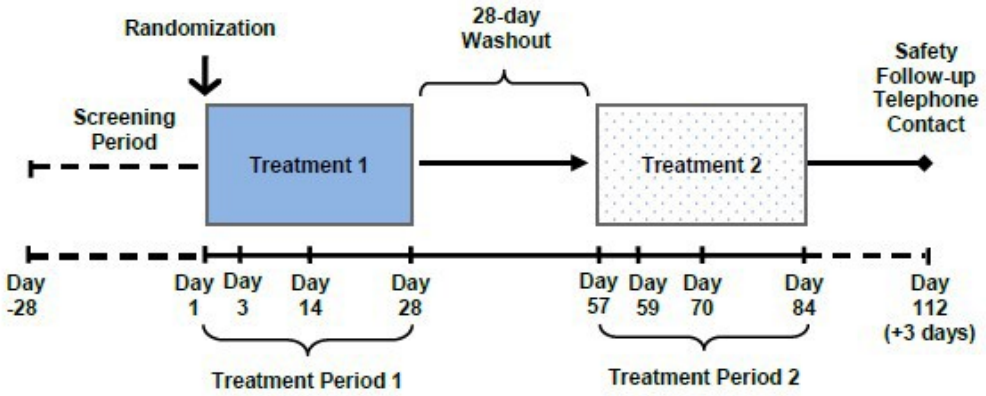
HS: 4.2% saline; Placebo: 0.17% saline

A schematic of the study design is provided in Figure 9-1. The study included a 28-day Run-in Period to ensure all subjects were on a stable Orkambi regimen (Orkambi+) without HS (HS-) before starting Treatment Period 1. Subjects who were Orkambi+/HS- at screening did not require a Run-in Period. All other subjects had a Run-in Period to become Orkambi+/HS-. Once Orkambi+, all subjects were treated with two Orkambi tablets (each containing LUM 200 mg/IVA 125 mg) orally every 12 hours (q12h) in the fed state.

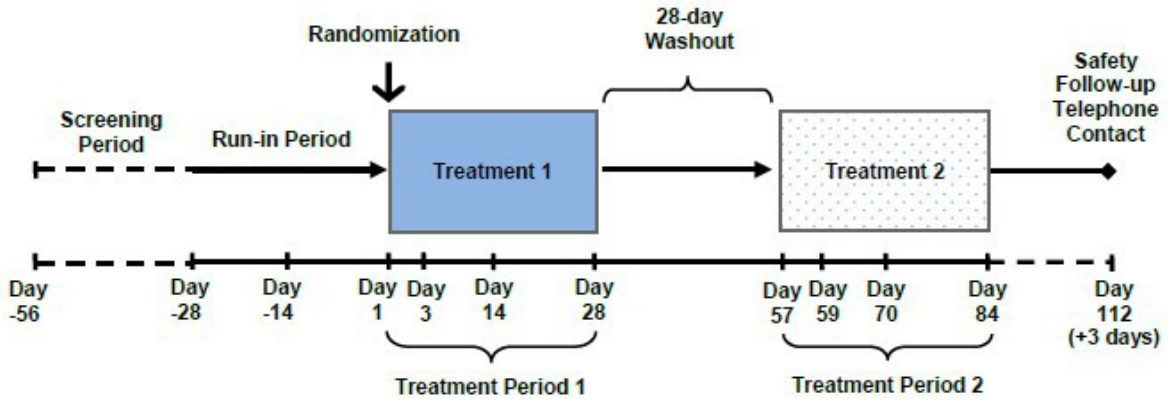
Once subjects were Orkambi+/HS-, they were to progress through Treatment Period 1 (28 days), Washout (28 days), and Treatment Period 2 (28 days) based on their randomized treatment sequence and were to have a safety follow-up telephone contact at 28 ± 3 days after the end of Treatment Period 2. Inhaled study drug was to be administered twice per day (bid) approximately 10 to 12 hours apart using a Sponsor-provided nebulizer for oral inhalation.

Figure 9-1 Schematic of Study Design

A. For Orkambi+/HS- Subjects



B. For Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ Subjects



Safety data were analyzed by inhaled study drug treatment. The Treatment-emergent (TE) Period for each treatment was defined as the time from first dose through the safety follow-up or 28 days after the last dose, whichever came first.

Study population /Sample size

Inclusion criteria:

Subjects who meet all of the following inclusion criteria will be eligible.

1. Subject (or subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, where appropriate, assent form.

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

3. Willing and able to use the nebulization device as directed by the study manual.

4. Subjects (male and female) will be aged 12 years or older on the date of ICF or, where appropriate, date of assent.

5. Subjects with confirmed diagnosis of CF,36 defined as a sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis. A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional. If both results are available, the result from the Screening Visit will be used to determine eligibility.

6. Subjects who are homozygous for F508del-CFTR. If the CFTR screening genotype result is not received before randomization, a previous CFTR genotype lab report may be used to establish eligibility. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study.

7. Subjects with ppFEV1 of ≥ 40 to <90 percentage points adjusted for age, sex, and height according to the Global Lung Initiative (GLI)37 at the Screening Visit.

8. Subjects with stable CF disease as deemed by the investigator.

9. Subjects who are willing to remain on a stable CF medication regimen through the Safety Follow-up Telephone Contact.

10. Subjects who are willing to discontinue physician-prescribed HS use.

11. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of inhaled study drug.

12. Subjects of childbearing potential and who are sexually active must meet the contraception requirements.

There were 147 subjects who entered the study, including 55 pediatric subjects aged ≥12 to <18 years of age. Of the 147 subjects, 35 were being treated with Orkambi and were not being treated with HS at Screening; these subjects proceeded directly to randomization. The remaining 112 subjects entered the Run-in Period to either establish a stable Orkambi regimen and/or washout of HS.

Of the 112 subjects who entered the Run-in Period, 5 subjects discontinued from the study (4 subjects were screen failures; 1 subject failed to meet an inclusion criterion) and 107 subjects continued to randomization. Thus, 142 subjects were randomized to 1 of 4 treatment sequences

Exclusion criteria:pertaining to liver, renal dysfunction, transplantations, co morbidities, long QT were also defined.

147 subjects will be randomized to 1 of 4 treatment sequences when they are determined to have met all eligibility criteria. Subjects will be randomized in a 2:2:1:1 ratio (VX-371 + 4.2% HS versus 4.2% HS; 4.2% HS versus VX-371 + 4.2% HS; VX-371 + placebo versus placebo; placebo versus VX-371 + placebo), stratifying for ppFEV1 severity (<70% or ≥70%).

Treatments

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH/LOT NUMBERS

• 85 µg VX-371 diluted in 3 mL 4.2% saline (batch numbers 00415D; 6B49)

• 3 mL 4.2% saline (batch numbers 00415B; 6B47)

• 85 µg VX-371 diluted in 3 mL 0.17% saline (batch numbers 00415C; 6B48)

• 3 mL 0.17% saline (batch numbers 00415A; 6B46)

• LUM 200 mg/IVA 125 mg tablets (batch numbers B16141; 6054025)

Inhaled study drug (VX-371, 4.2% saline [HS], and 0.17% saline [placebo]) was administered by oral nebulized inhalation. Orkambi was administered orally.

Inhaled study drug was administered bid approximately 10 to 12 hours apart by a PARI eFlow nebulizer. The nebulizer device (nebulizer and handset) were provided to the subject for use with the inhaled study drug at the Day 1 Visit. This nebulizer has been customized to be used only with the inhaled study drug and is not to be used for the inhalation of other treatments. Additionally, it is important that the subjects use the provided nebulizer for inhalation of study drug and not use any other PARI eFlow devices that they may have.

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

Blinding: The subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded

Duration of treatment: Excluding the Screening Period, the planned study duration was up to 115 days for Orkambi+/HS- subjects and up to 143 days for all other (Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+) subjects.

Outcomes/endpoints

Primary Endpoints

• Results of safety and tolerability assessments of adverse events (AEs), spirometry, clinical laboratory values (urine, serum, and plasma chemistry, hematology, and coagulation studies), standard 12-lead ECGs, vital signs, and ophthalmologic examinations

• Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline at Day 28 in each Treatment Period

Secondary Endpoint

• PK parameters for VX-371

Other Endpoints

• Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at 28 days of treatment

• Absolute change in weight from baseline at 28 days of treatment

• Absolute change in body mass index (BMI) from baseline at 28 days of treatment

• Pulmonary exacerbations

• PK parameter estimation of LUM and IVA

Statistical Methods

The primary efficacy endpoint is the absolute change in ppFEV1 from study baseline to the Day 28 measurements in each Treatment Period. The null hypothesis to be tested is that the mean change from study baseline in ppFEV1 to the Day 28 measurements is the same for VX-371 in combination with HS versus HS alone.

To have a feasible sample size and study duration, this study uses a crossover design. Assuming a standard deviation (SD) of 7 percentage points, 50 subjects per sequence are needed to have an approximately 81% power to detect a 3 percentage point treatment difference in the mean absolute change in ppFEV1 from study baseline at Day 28 between VX-371 + HS and HS alone. The study will have an approximately 80% power to detect a 3 percentage point (within treatment) change from baseline at Day 28 in ppFEV1 for VX-371. A 2-sided significance level of 0.05 was used in the sample size calculations. The sample size also takes into consideration an assumed dropout rate of 10%.

Summary statistics of the absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline at Day 28, and treatment-emergent AEs by pre-specified subgroups (including age at screening [≥ 12 to <18 years; ≥ 18 years]), were provided.

Results

Recruitment / Number analysed

A total of 26 subjects discontinued treatment. During Treatment Period 1, 10 subjects discontinued treatment, 7 of whom were due to an adverse event (AE). A total of 7 subjects discontinued during the Washout Period. Of the 125 subjects who entered Treatment Period 2, 9 subjects discontinued treatment, 5 of whom were due to an AE. Overall, 116 (81.7%) randomized subjects completed both treatment periods.

Efficacy results

The primary efficacy endpoint was the absolute change from study baseline in ppFEV1 at Day 28 in each Treatment Period. There was no statistically significant difference in ppFEV1 at Day 28 between any of the following groups:

- VX-371 + HS versus HS
- VX-371 + HS versus placebo
- VX-371 + HS versus VX-371 + placebo
- VX-371 + placebo versus placebo

No treatment-related difference for any pre-specified subgroups (based on baseline ppFEV1, age, gender, and region) was observed.

No statistically significant difference between VX-371 + HS versus HS or VX-371 + placebo versus placebo was observed in the absolute change in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 28. No clinically meaningful trends between VX-371 + HS versus HS or VX-371 + placebo versus placebo were observed for weight, body mass index, or pulmonary exacerbations.

Plasma and urine concentrations of VX-371 were low for both VX-371 + HS and VX-371 + placebo treatments.

Safety results

Overall, treatment with inhaled study drugs was generally safe and well-tolerated. There were no deaths and no subject had a life-threatening AE. Twelve subjects had AEs during the treatment emergent period that led to study drug discontinuation. The overall incidence of AEs was similar across all treatments, and the most common AEs were typical of the clinical manifestations associated with CF. There were no clinically meaningful differences in AEs with respect to age, sex, and region. The number of AEs was low in each subgroup, and no concerning trends were observed. The incidence of subjects with serious adverse events (SAEs) across treatments ranged from 4.4% to 13.0%. No evidence of clinically important treatment-related trends was identified from clinical laboratory results, vital signs assessments, ECGs, physical examinations, or ophthalmologic examinations.

Table 12-3 Adverse Events Occurring in >2 Subjects During the Treatment-emergent Period for At Least 1 Treatment (Safety Set)

System Organ Class Preferred Term	VX-371 + HS N = 89 n (%)	HS N = 90 n (%)	VX-371 + Placebo N = 46 n (%)	Placebo N = 42 n (%)
Subjects with Any TEAEs	**65 (73.0)**	**66 (73.3)**	**32 (69.6)**	**28 (66.7)**
Respiratory, thoracic, and mediastinal disorders	**45 (50.6)**	**38 (42.2)**	**24 (52.2)**	**13 (31.0)**
Cough	20 (22.5)	13 (14.4)	13 (28.3)	5 (11.9)
Oropharyngeal pain	8 (9.0)	6 (6.7)	4 (8.7)	1 (2.4)
Nasal congestion	7 (7.9)	5 (5.6)	2 (4.3)	1 (2.4)
Respiration abnormal	7 (7.9)	6 (6.7)	3 (6.5)	2 (4.8)
Wheezing	6 (6.7)	2 (2.2)	0	1 (2.4)
Haemoptysis	5 (5.6)	8 (8.9)	6 (13.0)	5 (11.9)
Sputum increased	5 (5.6)	2 (2.2)	5 (10.9)	2 (4.8)
Dyspnoea	3 (3.4)	3 (3.3)	2 (4.3)	1 (2.4)
Paranasal sinus hypersecretion	3 (3.4)	1 (1.1)	1 (2.2)	0
Productive cough	3 (3.4)	2 (2.2)	1 (2.2)	2 (4.8)
Rhinorrhoea	3 (3.4)	2 (2.2)	0	1 (2.4)
Infections and infestations	**22 (24.7)**	**32 (35.6)**	**14 (30.4)**	**12 (28.6)**
Infective pulmonary exacerbation of cystic fibrosis	11 (12.4)	15 (16.7)	10 (21.7)	6 (14.3)
Upper respiratory tract infection	3 (3.4)	1 (1.1)	1 (2.2)	1 (2.4)
Vulvovaginal mycotic infection	3 (3.4)	0	0	0
Nasopharyngitis	0	5 (5.6)	2 (4.3)	2 (4.8)
Investigations	**18 (20.2)**	**15 (16.7)**	**7 (15.2)**	**9 (21.4)**
ALT increased	4 (4.5)	5 (5.6)	0	4 (9.5)
Blood creatine phosphokinase increased	4 (4.5)	2 (2.2)	2 (4.3)	2 (4.8)
Blood potassium increased	4 (4.5)	4 (4.4)	2 (4.3)	1 (2.4)
AST increased	3 (3.4)	3 (3.3)	0	2 (4.8)
Pulmonary function test decreased	0	0	3 (6.5)	0
Gastrointestinal disorders	**12 (13.5)**	**16 (17.8)**	**5 (10.9)**	**2 (4.8)**
Diarrhoea	5 (5.6)	4 (4.4)	2 (4.3)	1 (2.4)
Abdominal pain	2 (2.2)	4 (4.4)	1 (2.2)	0
Nausea	2 (2.2)	3 (3.3)	3 (6.5)	0
Vomiting	1 (1.1)	6 (6.7)	1 (2.2)	0

System Organ Class Preferred Term	VX-371 + HS N = 89 n (%)	HS N = 90 n (%)	VX-371 + Placebo N = 46 n (%)	Placebo N = 42 n (%)
Nervous system disorders	**11 (12.4)**	**11 (12.2)**	**5 (10.9)**	**1 (2.4)**
Headache	6 (6.7)	8 (8.9)	2 (4.3)	1 (2.4)
Dysgeusia	3 (3.4)	0	1 (2.2)	0
General disorders and administration site conditions	**6 (6.7)**	**11 (12.2)**	**5 (10.9)**	**5 (11.9)**
Fatigue	2 (2.2)	4 (4.4)	1 (2.2)	0
Pyrexia	1 (1.1)	5 (5.6)	5 (10.9)	5 (11.9)
Immune system disorders	**4 (4.5)**	**0**	**1 (2.2)**	**1 (2.4)**
Seasonal allergy	3 (3.4)	0	1 (2.2)	1 (2.4)

One subject had SAEs of increased alanine aminotransferase, aspartate aminotransferase, and blood creatine phosphokinase that, in the opinion of the investigator, could have been attributed to Orkambi. There were no new safety issues identified for Orkambi

2.2.3. **Discussion on clinical aspects**

Study VX15-371-101 was a crossover study designed to evaluate the safety, efficacy, and PK of treatment with VX-371 + HS compared to HS alone in subjects with CF who were ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi. Two additional crossover treatment sequences allowed for the comparison of VX-371 + placebo versus placebo alone.

The efficacy of Orkambi was not evaluated as part of this study. Therefore, no additional data related to the efficacy of Orkambi was generated from this study, although it was used as baseline treatment in all patients. The study did not produce any new safety signals with regard to Orkambi either.

Main conclusions:

There was no statistically significant difference between VX-371 + HS versus HS alone, VX-371 + placebo, or placebo in the primary efficacy endpoint of absolute change in ppFEV1 from baseline at Day 28. There was no statistically significant difference between VX 371 + placebo versus placebo in the absolute change in ppFEV1 from baseline at Day 28.

• There was no statistically significant difference between VX-371 + HS versus HS or VX-371 + placebo versus placebo in the absolute change in the CFQ-R respiratory domain from baseline at Day 28.

• Treatment with inhaled study drugs was safe and well-tolerated, with most AEs consistent with the expected manifestations for CF disease. There were no new safety issues identified for Orkambi.

3. Rapporteur's overall conclusion and recommendation

This phase 2a study was not intended to evaluate Orkambi but to evaluate the safety, efficacy, and PK of treatment with VX-371 + HS compared to HS alone in subjects with CF who were ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi. 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.