Clinical Overview

ORKAMBI® (lumacaftor/ivacaftor) in patients 12 years of age and older who are homozygous for the *F508del* mutation[1]

INDICATIONS AND USAGE

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene.

Limitations of Use

The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation.

Click here for Important Safety Information and full Prescribing Information.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets
100/125 mg • 150/188 mg oral granules

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Important Safety Information

USE IN PATIENTS WITH ADVANCED LIVER DISEASE

- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI® (lumacaftor/ivacaftor)
- Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced

LIVER-RELATED EVENTS

- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve
- Dosing should be interrupted in patients with ALT or AST greater than 5 x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations greater than 3 x ULN when associated with bilirubin elevations greater than 2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

RESPIRATORY EVENTS

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted FEV_1 ($ppFEV_1$) <40). Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

EFFECT ON BLOOD PRESSURE

- Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI

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Important Safety Information (cont)

DRUG INTERACTIONS

Substrates of CYP3A

- Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI® (lumacaftor/ivacaftor) may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended
- ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI

Strong CYP3A Inducers

- Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended

CATARACTS

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with ORKAMBI

ADVERSE REACTIONS

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients
- The most common adverse reactions in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza
- The safety profile in patients age 6 through 11 years from an open-label Phase 3 trial (Trial 3; N=58) and a placebo-controlled Phase 3 trial (Trial 4; patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and sputum increased. The safety profile in patients age 2 through 5 years from an open-label Phase 3 trial (Trial 6; N=60) was similar to that in patients aged 6 years and older

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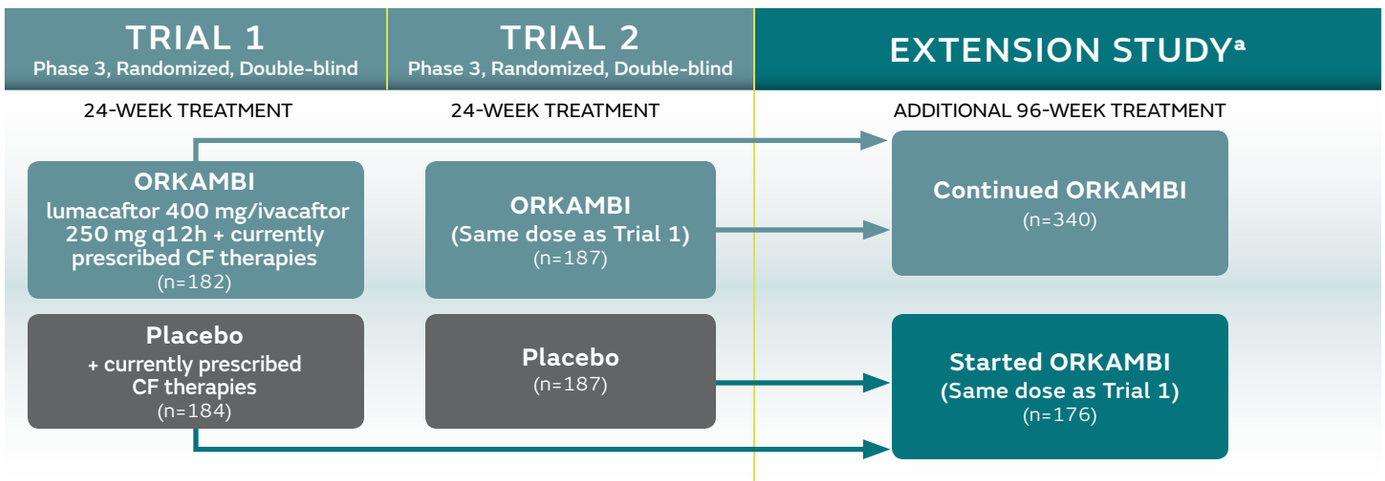
ORKAMBI® (lumacaftor/ivacaftor) studied in patients age 12 years and older[1-5]



PRIMARY ENDPOINT

- Absolute change in ppFEV$_1$ from baseline at Week 24

- Safety of long-term treatment based on adverse events, clinical laboratory values, standard digital electrocardiograms, vital signs, and pulse oximetry

SELECTED SECONDARY ENDPOINTS

Listed in order evaluated by statistical analyses hierarchy:

- Relative change in ppFEV$_1$, absolute change in BMI, absolute change in CFQ-R Respiratory Domain score, proportion of patients with ≥5% relative change in ppFEV$_1$, and number of pulmonary exacerbations

- Absolute change from baseline in percent predicted FEV$_1$
- Absolute change from baseline in BMI
- Absolute change from baseline in the CFQ-R Respiratory Domain score
- Number of pulmonary exacerbations

POOLED ANALYSIS

- The safety of ORKAMBI was evaluated based on a prespecified pooled analysis
- A separate pooled analysis for efficacy was not prespecified and did not correct for multiple comparisons. Separate analyses of Trials 1 and 2 were conducted to evaluate efficacy

ANALYSES

- The primary analysis of the Extension Study included data through 72 weeks. A sensitivity analysis was performed including data through 96 weeks
- For the ORKAMBI-to-ORKAMBI group in the Extension Study, baseline from Trials 1 and 2 was used. For the placebo-to-ORKAMBI group, baseline from treatment initiation in the Extension Study was used

KEY INCLUSION CRITERIA

- ≥12 years old
- Confirmed CF diagnosis
- Clinically stable
- *F508del* homozygous
- Percent predicted FEV$_1$ (ppFEV$_1$) 40 to 90 at screening

- Completed Trial 1 or Trial 2

KEY EXCLUSION CRITERIA

- History of colonization with organisms such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*
- 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 x ULN, or total bilirubin ≥2 x ULN)

- Any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering the study drug to the participant
- History of drug intolerance
- History of poor compliance with the study drug

[a]At the start of the Extension Study, patients who received placebo during Trials 1 and 2 were randomized 1:1 to ORKAMBI or lumacaftor 600 mg qd/ivacaftor 250 mg q12h. 334 patients continued to receive lumacaftor 600 mg qd/ivacaftor 250 mg q12h, and 179 rolled over from receiving placebo to lumacaftor 600 mg qd/ivacaftor 250 mg q12h.[4]

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire-Revised; GGT, gamma-glutamyl transpeptidase; qd, once daily; q12h, every 12 hours.

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ORKAMBI® (lumacaftor/ivacaftor) studied in patients age 12 years and older[1-5] (cont)

EXTENSION STUDY[a,b]

ADDITIONAL 96-WEEK TREATMENT

Continued ORKAMBI
(n=340)

Started ORKAMBI
(Same dose as Trial 1)
(n=176)

RATE OF CHANGE ANALYSIS[4]

Cohort treated with ORKAMBI
(n=455)[c]

Propensity-score matched controls
(n=1588)

Cohorts

- Patients receiving ORKAMBI in Trial 1, Trial 2, and Extension Study
- Propensity-score matched control patients homozygous for the *F508del* mutation based on observational data from the US CFFPR

Objective

- To evaluate whether treatment with ORKAMBI affects the rate of change in pulmonary function in patients 12 years and older who are homozygous for the *F508del* mutation

- A matched cohort of 1588 patients from the US CFFPR was used as the comparator because there was no placebo group in the Extension Study[4]
- A propensity-score approach was used to match the two groups on known predictors of disease progression[4]
  - Propensity scoring is a statistical matching technique used in observational research that attempts to balance the study groups to make them as similar as possible[7]
- Patients contributed the following amount of data[8]:
  - ORKAMBI: 436 (95.8%) patients had ≥48 weeks of data; 407 (89.5%) had ≥72 weeks of data; 276 (60.7%) had ≥96 weeks of data
  - CONTROL: 1570 (98.9%) patients had ≥48 weeks of data; 1518 (95.6%) had ≥72 weeks of data; 1035 (65.2%) had ≥96 weeks of data

[a]368 patients received lumacaftor 600 mg qd/ivacaftor 250 mg q12h. The focus of the following data is the approved dose of ORKAMBI: lumacaftor 400 mg/ivacaftor 250 mg q12h.[1,4]

[b]At the start of the Extension Study, patients who received placebo during Trials 1 and 2 were randomized 1:1 to ORKAMBI or lumacaftor 600 mg qd/ivacaftor 250 mg q12h. 334 patients continued to receive lumacaftor 600 mg qd/ivacaftor 250 mg q12h, and 179 rolled over from receiving placebo to lumacaftor 600 mg qd/ivacaftor 250 mg q12h.[4]

[c]24 patients taking ORKAMBI had no identified match among CFFPR controls and therefore were not included in the analysis. Nearly half of the patients taking ORKAMBI (n=213, 46.8%) were matched to 5 control patients.[6]

CFFPR, Cystic Fibrosis Foundation Patient Registry.

Trials 1 and 2 in patients age 12 years and older

Improved and sustained lung function and other key clinical outcomes[1,2]

- In each trial, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs placebo. For an endpoint to be significant, both it and all previous tests had to achieve $P \leq 0.025$[1,2]
  - The shaded boxes in the table below indicate which endpoints were statistically significant as confirmed by the hierarchical testing procedure. Other efficacy measures were not considered statistically significant
- The pooled analysis for efficacy was not prespecified and did not correct for multiple comparisons[1,2]

		TRIAL 1[1,2]		TRIAL 2[1,2]		POOLED[2]	
		ORKAMBI® (lumacaftor/ivacaftor) (n=187)	**Placebo** (n=184)	**ORKAMBI** (n=187)	**Placebo** (n=187)	**ORKAMBI** (n=369)	**Placebo** (n=371)
PRIMARY ENDPOINT							
Absolute change in percent predicted FEV_1 at Week 24 (percentage points)[a]	Treatment difference (95% CI)	2.6 (1.2, 4.0) *P*=0.0003	—	3.0 (1.6, 4.4) *P*<0.0001	—	2.8 (1.8, 3.8)	—
KEY SECONDARY ENDPOINTS							
Relative change in percent predicted FEV_1 at Week 24 (percentage)[a]	Treatment difference (95% CI)	4.3 (1.9, 6.8) *P*=0.0006	—	5.3 (2.7, 7.8) *P*<0.0001	—	4.8 (3.0, 6.6)	—
Absolute change in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI)	0.1 (-0.1, 0.3)	—	0.4 (0.2, 0.5) *P*=0.0001	—	0.2 (0.1, 0.4)	—
Absolute change in CFQ-R Respiratory Domain score at Week 24 (points)	Treatment difference (95% CI)	1.5 (-1.7, 4.7)	—	2.9 (-0.3, 6.0)	—	2.2 (0.0, 4.5)	—
Proportion of patients with ≥5% relative change in percent predicted FEV_1 at Week 24[a]	%	37%	22%	41%	23%	39%	22%
	Odds ratio (95% CI)	2.1 (1.3, 3.3)	—	2.4 (1.5, 3.7)	—	2.2 (1.6, 3.1)	—
Number of pulmonary exacerbations through Week 24[b]	No. of events (rate per 48 weeks)	73 (0.7)	112 (1.1)	79 (0.7)	139 (1.2)	152 (0.7)	251 (1.1)
	Rate ratio (95% CI)	0.7 (0.5, 0.9)	—	0.6 (0.4, 0.8)	—	0.6 (0.5, 0.8)	—

[a]Assessed as the average of the treatment effects at the Week 16 and Week 24 time points.[1]

[b]A pulmonary exacerbation was defined as a new or change in antibiotic therapy (IV, inhaled, or oral) associated with 4 or more of the following 12 prespecified sinopulmonary signs/symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature >38°C (100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical chest exam; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection.[2]

IV, intravenous.

IMPORTANT SAFETY INFORMATION

Use in Patients With Advanced Liver Disease

- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI
- Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced

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Trials 1 and 2 in patients age 12 years and older

Safety demonstrated in >1100 patients in two Phase 3 trials

THE OVERALL SAFETY PROFILE OF ORKAMBI® (lumacaftor/ivacaftor) IS BASED ON POOLED DATA FROM TRIALS 1 AND 2[1]

Discontinuations due to adverse events[1]

- ORKAMBI 5%; placebo 2%

Serious adverse reactions[1]

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included those below. These occurred in 1% or less of patients:
  - Pneumonia
  - Hemoptysis
  - Increased blood creatine phosphokinase
  - Cough
  - Transaminase elevations

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Trials 1 and 2 in patients age 12 years and older

Safety profile

LIVER-RELATED ADVERSE REACTIONS[1]

- In Trials 1 and 2, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was similar between patients treated with ORKAMBI® (lumacaftor/ivacaftor) and those who received placebo
- Three patients who received ORKAMBI had liver-related serious adverse reactions, including two reported as transaminase elevations and one as hepatic encephalopathy, compared to none in the placebo group
  - Of these three, one had elevated transaminases (>3 x ULN) associated with bilirubin elevation >2 x ULN. Following discontinuation or interruption of ORKAMBI, transaminases decreased to <3 x ULN
- Among six patients with preexisting cirrhosis and/or portal hypertension who received ORKAMBI, worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy was observed in one patient
  - The event occurred within 5 days of the start of dosing and resolved following discontinuation of ORKAMBI

RESPIRATORY ADVERSE REACTIONS

- In Trials 1 and 2, the incidence of respiratory symptom-related adverse reactions (i.e., chest discomfort, dyspnea, and respiration abnormal) was more common in patients treated with ORKAMBI (22%) compared to patients who received placebo (14%)[1]
  - Respiration abnormal (chest tightness): ORKAMBI (9%) vs placebo (6%)
  - Dyspnea: ORKAMBI (13%) vs placebo (8%)
  - The incidence of these adverse reactions was more common in patients treated with ORKAMBI with lower pre-treatment FEV_1
- Most respiratory symptom-related adverse events occurred within the first week of treatment and resolved within 2 weeks[2]
- During a 24-week, open-label, Phase 3b clinical trial in 46 patients aged 12 years and older (Trial 5) with advanced lung disease ($ppFEV_1$ <40) [mean $ppFEV_1$ 29.1 at baseline (range: 18.3 to 42.0)], the incidence of respiratory symptom-related adverse reactions was 65%

MENSTRUAL ABNORMALITIES[1]

- In Trials 1 and 2, the incidence of combined menstrual abnormality adverse reactions (e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular) was more common in female patients treated with ORKAMBI (10%) compared to placebo (2%)
- These events occurred more frequently in the subset of female patients treated with ORKAMBI who were using hormonal contraceptives (27%) compared to those not using hormonal contraceptives (3%)

INCREASED BLOOD PRESSURE[1]

- In Trials 1 and 2, adverse reactions related to increases in blood pressure (e.g., hypertension, blood pressure increased) were reported in 1.1% (4/369) of patients treated with ORKAMBI and in no patients who received placebo
- The proportion of patients who experienced a systolic blood pressure value >140 mm Hg or a diastolic blood pressure >90 mm Hg on at least two occasions was 3.6% and 2.2% in patients treated with ORKAMBI, respectively, compared with 1.6% and 0.5% in patients who received placebo

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Trials 1 and 2 in patients age 12 years and older

Safety profile (cont)

Adverse Reactions in ≥5% of Patients Treated With ORKAMBI® (lumacaftor/ivacaftor) and at a Higher Rate Than Placebo[1]		
Adverse Reaction (Preferred Term)	**ORKAMBI** N=369 (%)	**Placebo** N=370 (%)
Dyspnea	48 (13)	29 (8)
Nasopharyngitis	48 (13)	40 (11)
Nausea	46 (13)	28 (8)
Diarrhea	45 (12)	31 (8)
Upper respiratory tract infection	37 (10)	20 (5)
Fatigue	34 (9)	29 (8)
Respiration abnormal[a]	32 (9)	22 (6)
Blood creatine phosphokinase increased	27 (7)	20 (5)
Rash	25 (7)	7 (2)
Flatulence	24 (7)	11 (3)
Rhinorrhea	21 (6)	15 (4)
Influenza	19 (5)	8 (2)

[a]Reported as chest tightness.[2]

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Extension Study in patients age 12 years and older

Safety profile at 96 weeks consistent with Trials 1 and 2[4]

PATIENT DISPOSITION[10]

- 215 of 516 patients enrolled and completed 96 weeks of treatment in the Extension Study, including:
  - 142 of 340 patients (41.8%) in the ORKAMBI-to-ORKAMBI group and 73 of 176 patients (41.5%) in the placebo-to-ORKAMBI group
- Discontinuations due to adverse events were reported in 20 patients (5.9%) in the ORKAMBI-to-ORKAMBI group and 18 patients (10.2%) in the placebo-to-ORKAMBI group
- 263 patients transitioned off clinical study drug or discontinued for reasons other than adverse events. The majority of these occurred between Weeks 72 and 96 of the Extension Study

SAFETY WAS THE PRIMARY ENDPOINT

- Three deaths occurred across both dose groups; none were considered to be related to the study drug by the study investigators[4]
  - One was considered to be related to a pulmonary exacerbation event, 1 was related to respiratory failure concurrent with a pulmonary exacerbation event, and 1 was attributed to distal intestinal obstruction syndrome (DIOS)
- Overall, 42% of patients in the ORKAMBI-to-ORKAMBI group and 51% of patients in the placebo-to-ORKAMBI group reported serious adverse events during the 96-week Extension Study[11]
  - Serious adverse events reported with ORKAMBI® (lumacaftor/ivacaftor) in the Extension Study were consistent with those reported in Trials 1 and 2 and were predominantly CF complications
  - Most frequently reported serious adverse events were pulmonary exacerbation, hemoptysis, and DIOS
  - Serious adverse events occurring at a frequency of 1% to 2% were pneumonia, influenza, and CF-related diabetes
- An increase in blood pressure was observed at Week 96[4]
  - In the ORKAMBI-to-ORKAMBI group, mean blood pressure increased from 113.4/68.7 mm Hg at the baseline of Trials 1 and 2 to 118.0/72.8 mm Hg at Week 96 of the Extension Study[4]
  - In the placebo-to-ORKAMBI group, mean blood pressure increased from 113.2/68.6 mm Hg at the baseline of Trials 1 and 2 to 119.1/73.5 mm Hg at Week 96 of the Extension Study[12]
  - Monitoring of blood pressure is recommended in patients treated with ORKAMBI[1]

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Extension Study in patients age 12 years and older

Safety profile at 96 weeks consistent with Trials 1 and 2[4] (cont)

Summary of Adverse Events for the Extension Study (≥10% In Any Group)[9]		
Adverse Reaction, n (%)	**ORKAMBI-to-ORKAMBI** (n=340)	**Placebo-to-ORKAMBI** (n=176)
Infective pulmonary exacerbations of CF	217 (64)	116 (66)
Cough	145 (43)	82 (47)
Sputum increased	79 (23)	37 (21)
Hemoptysis	72 (21)	32 (18)
Headache	56 (17)	22 (13)
Dyspnea	53 (16)	36 (21)
Pyrexia	47 (14)	31 (18)
Nasopharyngitis	66 (19)	27 (15)
Diarrhea	42 (12)	28 (16)
Nausea	34 (10)	27 (15)
Respiration abnormal[a]	35 (10)	27 (15)
Upper respiratory tract infection	49 (14)	29 (17)
Oropharyngeal pain	44 (13)	22 (13)
Fatigue	36 (11)	22 (13)
Abdominal pain	34 (10)	16 (9)
Nasal congestion	37 (11)	23 (13)
Sinusitis	48 (14)	13 (7)
Influenza	27 (8)	18 (10)

[a]Reported as chest tightness.[2]

- The most common adverse events occurring in ≥20% of patients in either treatment group were pulmonary exacerbations, cough, sputum increased, hemoptysis, and dyspnea[9]

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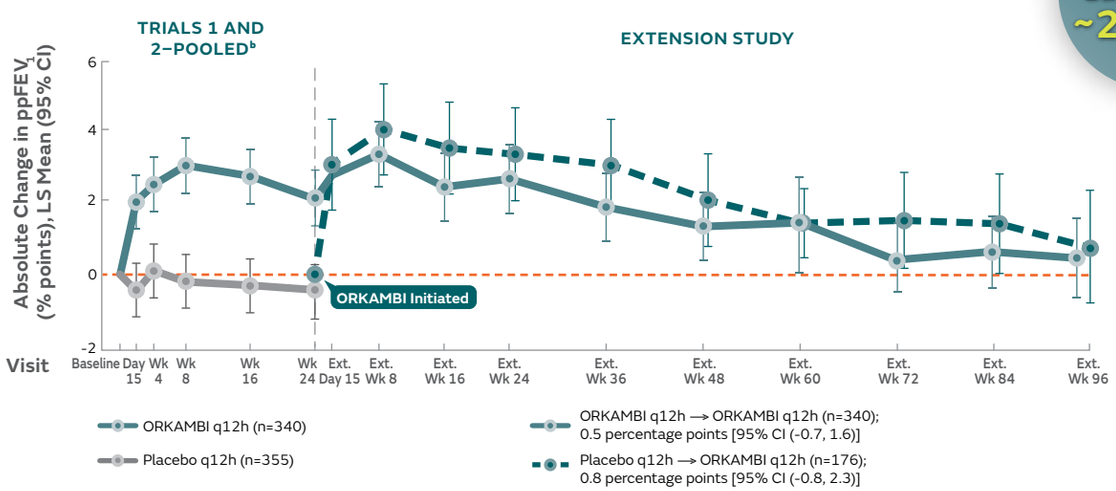
Extension Study in patients age 12 years and older

ORKAMBI® (lumacaftor/ivacaftor) demonstrated clinical benefits over time[4]

FEV_1 MAINTAINED ABOVE PRE-TREATMENT BASELINE FOR UP TO 120 WEEKS[4]

Mean Absolute Change in Percent Predicted FEV_1 in Patients Who Rolled Over From Trials 1 and 2 to the Extension Study[4,a]



Adapted from Konstan MW et al. *Lancet Respir Med.* 2017;5(2):107-118, with permission from Elsevier.

[a]Based on Wang-Hankinson calculation.

[b]Results are based on a pooled analysis that was not prespecified and includes only those patients who continued into the Extension Study.

CI, confidence interval; LS, least squares.

IMPORTANT SAFETY INFORMATION

Liver-related Events

- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve
- Dosing should be interrupted in patients with ALT or AST greater than 5 x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations greater than 3 x ULN when associated with bilirubin elevations greater than 2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

Please click here for Limitations of the Extension Study.

Click here for Important Safety Information and full Prescribing Information.

In patients age 12 years and older

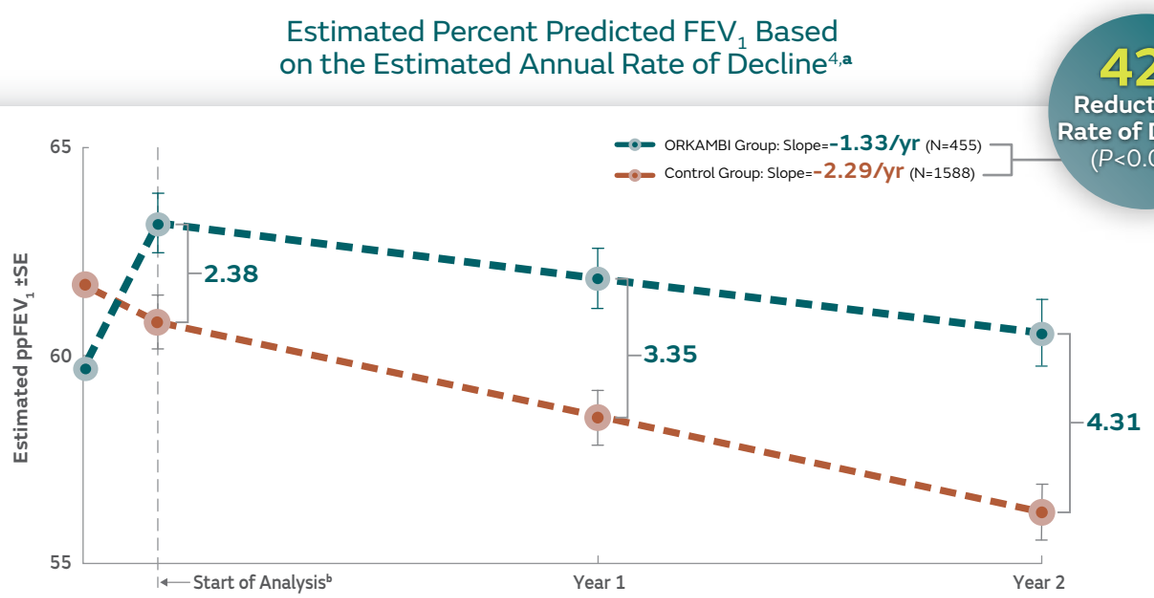
ORKAMBI® (lumacaftor/ivacaftor) rate of change analysis[4]

Rate of change analysis in patients age 12 years and older

REDUCED RATE OF LUNG FUNCTION DECLINE VS MATCHED CONTROLS SUGGEST THAT ORKAMBI MAY MODIFY THE COURSE OF DISEASE[4]

- No clear definition of disease modification has been established for CF

Estimated Percent Predicted FEV_1 Based on the Estimated Annual Rate of Decline[4,a]



Adapted from Konstan MW et al. *Lancet Respir Med.* 2017;5(2):107-118, with permission from Elsevier.

[a]Rate of decline analysis utilized GLI equations to calculate percent predicted FEV_1. Sensitivity analysis using Wang-Hankinson prediction formulas resulted in a similar relative difference between the groups.[4]

[b]Day 21 of Trials 1 and 2.[5]

GLI, Global Lung Function Initiative; SE, standard error.

IMPORTANT SAFETY INFORMATION

Respiratory Events

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted FEV_1 ($ppFEV_1$) <40). Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

Please click here for Limitations of the Rate of Change Analysis.

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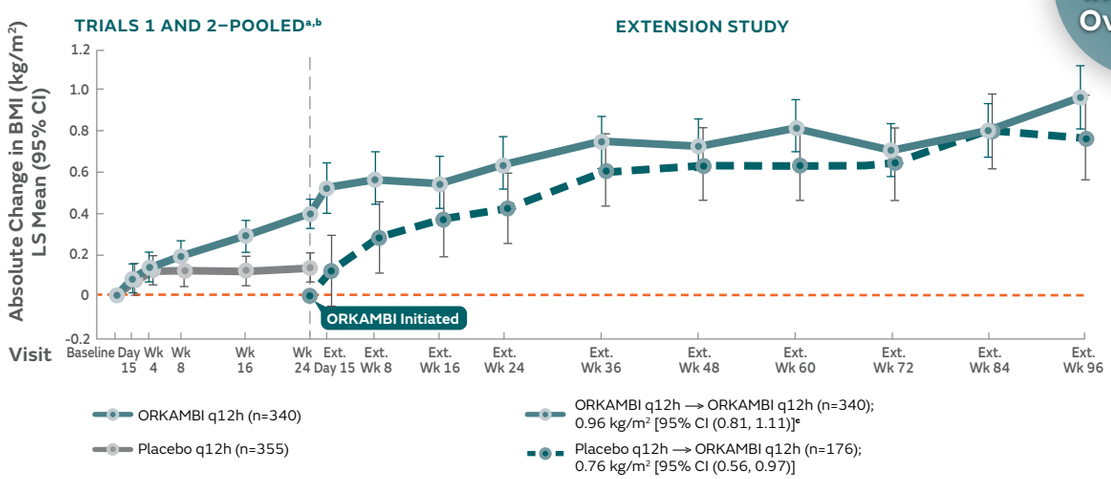
Extension Study in patients age 12 years and older

BMI improvements sustained for up to 120 weeks[4]

INCREASES IN MEAN BMI WERE SEEN IN BOTH ORKAMBI® (lumacaftor/ivacaftor) TREATMENT GROUPS[4]

Mean Absolute Change in BMI in Patients Who Rolled Over From Trials 1 and 2 to the Extension Study[4,a]

BMI Increased Over Time



Adapted from Konstan MW et al. *Lancet Respir Med.* 2017;5(2):107-118, with permission from Elsevier.

[a]In the individual analyses of these trials, changes were statistically significant with ORKAMBI vs placebo in Trial 2 ($P<0.0001$), but not statistically significant in Trial 1.[1]

[b]Results are based on a pooled analysis that was not prespecified and did not correct for multiple comparisons.

[c]Includes data from Trials 1 and 2.

IMPORTANT SAFETY INFORMATION

Effect on Blood Pressure

- Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI

Please click here for Limitations of the Extension Study.

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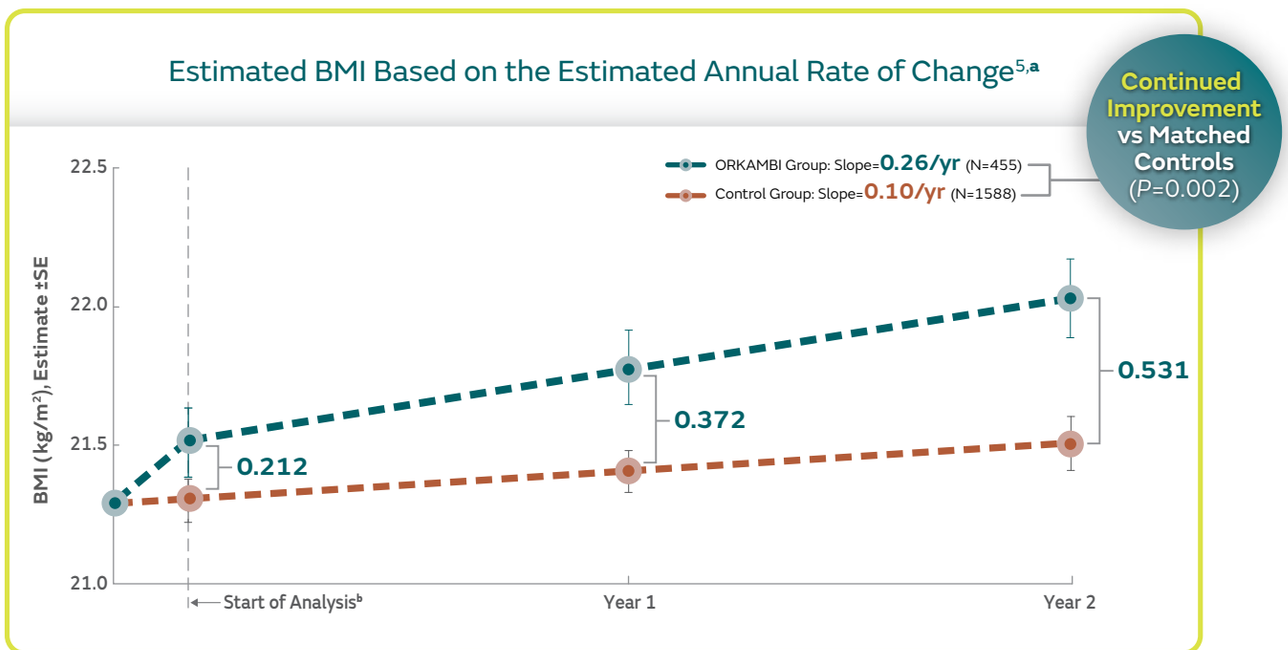
Rate of Change Analysis in patients age 12 years and older

Improved BMI rate of change vs matched controls[5]

ANALYSIS SUGGESTS ORKAMBI® (lumacaftor/ivacaftor) HAS A LONG-TERM IMPACT ON BMI



Adapted from Konstan MW et al. *Lancet Respir Med.* 2017;5(2)(suppl1-28):107-118, with permission from Elsevier.

[a]Post-baseline data limited to 2 years. Visits ≤21 days of initiation excluded.

[b]Day 21 of Trials 1 and 2.

IMPORTANT SAFETY INFORMATION

Use in Patients With Advanced Liver Disease

- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI
- Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced

Please click here for Limitations of the Rate of Change Analysis.

Click here for Important Safety Information and full Prescribing Information.

Trials 1 and 2 and Extension Study in patients age 12 years and older

Results for CFQ-R Respiratory Domain score

- In a pooled analysis of Trials 1 and 2, the mean treatment difference for the CFQ-R Respiratory Domain score at Week 24 was 2.2 points vs placebo [95% CI (0.0, 4.5)][2]*
  - In the individual analyses of these trials, changes were not statistically significant with ORKAMBI® (lumacaftor/ivacaftor) vs placebo in either trial
- At Week 96 of the Extension Study, the LS mean absolute change from baseline in the CFQ-R Respiratory Domain score was 3.5 points [95% CI (1.3, 5.8)] for the ORKAMBI-to-ORKAMBI group and 0.5 points [95% CI (-2.7, 3.6)] for the placebo-to-ORKAMBI group[4]

*Results are based on a pooled analysis that was not prespecified and did not correct for multiple comparisons.

Please click here for Limitations of the Extension Study.

IMPORTANT SAFETY INFORMATION

Drug Interactions

Substrates of CYP3A

- Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended
- ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI

Strong CYP3A Inducers

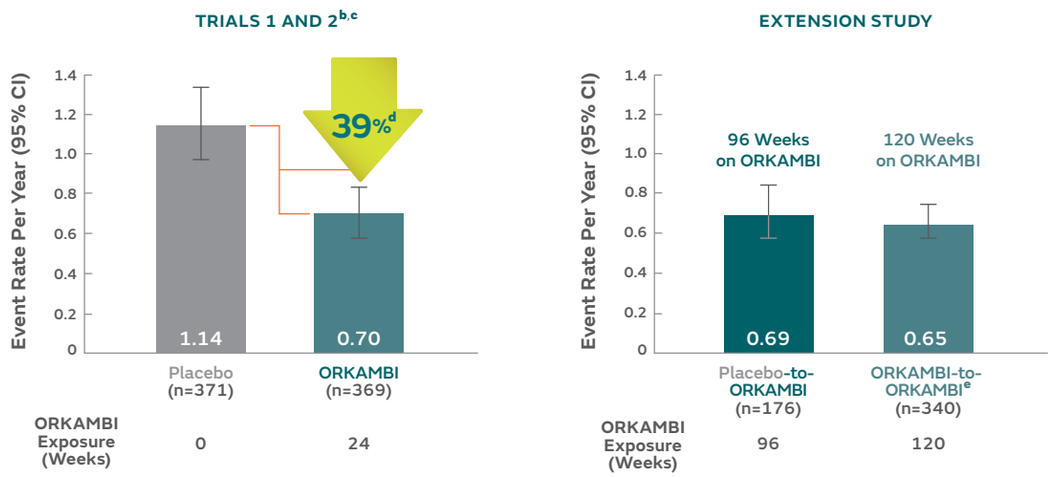
- Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended

Click here for Important Safety Information and full Prescribing Information.

Trials 1 and 2 and Extension Study in patients age 12 years and older

Reduced rate of pulmonary exacerbations maintained up to 120 weeks[2,4]

Annualized Pulmonary Exacerbation Rate[2,4,a]



Adapted from Konstan MW et al. *Lancet Respir Med.* 2017;5(2):107-118, with permission from Elsevier.

[a]The number of pulmonary exacerbations is expressed as a rate over 48 weeks. For Trials 1 and 2, this rate is based on 24 weeks of observation. For the Extension Study, this rate is based on the total number of weeks of ORKAMBI® (lumacaftor/ivacaftor) exposure.

[b]In the individual analyses of these trials, changes were not statistically significant with ORKAMBI vs placebo in Trials 1 or 2.[2]

[c]Results are based on a pooled analysis that was not prespecified and did not correct for multiple comparisons.

[d]Rate ratio for ORKAMBI vs placebo: 0.61, 95% CI (0.49, 0.76).

[e]Includes data from Trials 1 and 2.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients
- The most common adverse reactions in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza
- The safety profile in patients age 6 through 11 years from an open-label Phase 3 trial (Trial 3; N=58) and a placebo-controlled Phase 3 trial (Trial 4; patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and sputum increased. The safety profile in patients age 2 through 5 years from an open-label Phase 3 trial (Trial 6; N=60) was similar to that in patients aged 6 years and older

Please click here for Limitations of the Extension Study.

Click here for Important Safety Information and full Prescribing Information.

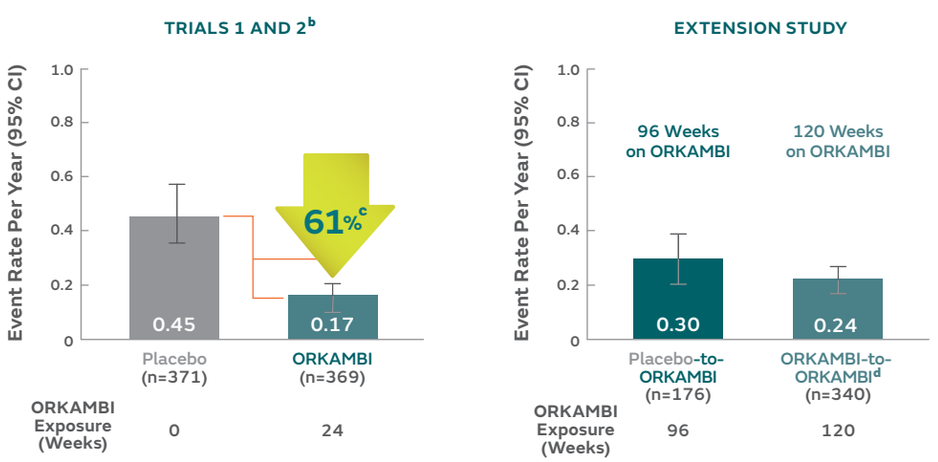
Trials 1 and 2 and Extension Study—Post Hoc Analysis in patients age 12 years and older

Reduced rate of hospitalizations due to pulmonary exacerbations maintained up to 120 weeks[2,4]

The results for **pulmonary exacerbations requiring hospitalization** included below are based on a post hoc analysis. This analysis did not ascertain whether findings were attributable to ORKAMBI® (lumacaftor/ivacaftor)[4,13]

- Number of pulmonary exacerbations through Week 24 was a secondary endpoint in Trials 1 and 2 and was not statistically significant in either trial[1]

Annualized Rate of Pulmonary Exacerbations Requiring Hospitalization[2,4,a]



Adapted from Konstan MW et al. *Lancet Respir Med.* 2017;5(2):107-118, with permission from Elsevier.

[a]The number of pulmonary exacerbations is expressed as a rate over 48 weeks. For Trials 1 and 2, this rate is based on 24 weeks of observation. For the Extension Study, this rate is based on the total number of weeks of ORKAMBI exposure.

[b]Results are based on a pooled analysis that was not prespecified and did not correct for multiple comparisons.

[c]Rate ratio for ORKAMBI vs placebo: 0.39, 95% CI (0.26, 0.56).[14]

[d]Includes data from Trials 1 and 2.

[e]Rate ratio for ORKAMBI vs placebo: 0.44, 95% CI (0.32, 0.59).[15]

Please click here for Limitations of the Extension Study.

IMPORTANT SAFETY INFORMATION

Cataracts

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with ORKAMBI

Click here for Important Safety Information and full Prescribing Information.

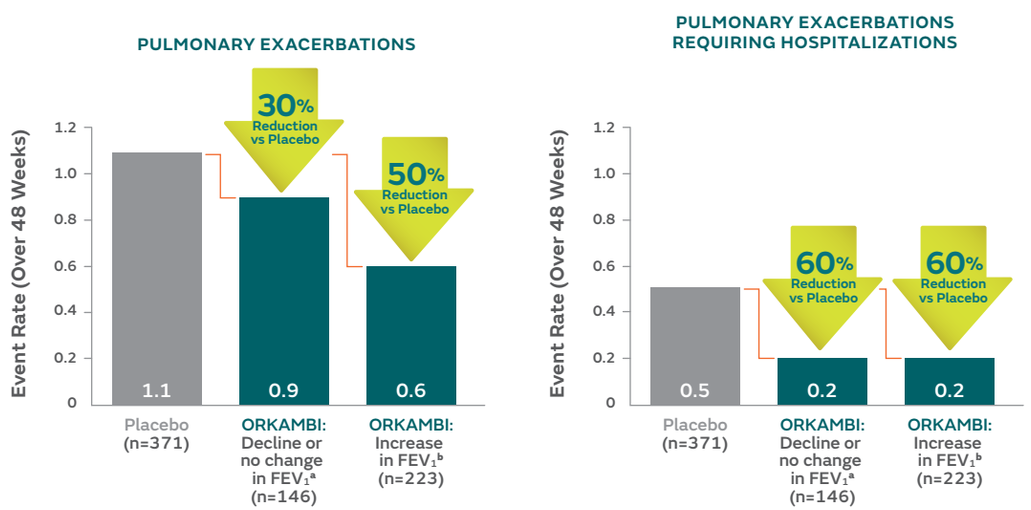
Trials 1 and 2—Post-Hoc Analysis in patients age 12 years and older

Reduced rate of pulmonary exacerbations regardless of changes in FEV_1[16]

These results are based on a post hoc analysis and therefore statistical significance cannot be determined. This analysis does not ascertain whether findings were attributable to ORKAMBI® (lumacaftor/ivacaftor).[13,16]

In patients with CF, pulmonary exacerbations are associated with FEV_1 decline. Therefore, to minimize this potential bias, the earliest post-baseline FEV_1 measure (at Day 15) was used to categorize lung function change in the ORKAMBI group.[16]

Pulmonary Exacerbation Event Rates and Rate Ratios at 24 Weeks by Absolute Change in FEV_1 (From Baseline to Day 15)[16]



The number of pulmonary exacerbations was reported through Week 24 and expressed as a rate over 48 weeks.

[a] In patients with a decline or no change in $ppFEV_1$, the rate ratio for ORKAMBI vs placebo was 0.7, 95% CI (0.6, 1.0) for pulmonary exacerbations and 0.4, 95% CI (0.2, 0.7) for pulmonary exacerbations requiring hospitalization.

[b] In patients with an increase in $ppFEV_1$, the rate ratio for ORKAMBI vs placebo was 0.5, 95% CI (0.4, 0.7) and 0.4, 95% CI (0.2, 0.6) for pulmonary exacerbations requiring hospitalization.

- There were also fewer pulmonary exacerbations requiring hospitalization, regardless of changes in percent predicted FEV_1[16]

IMPORTANT SAFETY INFORMATION

Respiratory Events

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted FEV_1 ($ppFEV_1$) <40). Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

Click here for Important Safety Information and full Prescribing Information.

Limitations and disclosures of the Extension Study and Rate of Change Analysis in patients age 12 years and older

LIMITATIONS OF THE EXTENSION STUDY

- Enrollment was limited only to those patients who met strict inclusion criteria, completed Trials 1 and 2, and elected to enroll in the Extension Study[4,5]
- The Extension Study was not a placebo-controlled study[4]
- All patients in the Extension Study knew they were on active drug, which may have introduced bias related to awareness of treatment[4]
- Trials 1 and 2 required patients to remain on their usual prescribed CF regimen. In the Extension Study, patients may have had changes in their stable medication regimen, but the data set was not large enough to assess the effect that changes in concomitant drugs could have had on the efficacy and safety profile of ORKAMBI® (lumacaftor/ivacaftor)[4]
- Although a relatively large study over a 96-week period, rare adverse events might not have been detected
- In patients with CF, pulmonary exacerbations and $ppFEV_1$, are interdependent. There are known methodological limitations in outcome stratification by covariates affected by treatment allocation; to address this issue, the earliest post-baseline $ppFEV_1$ measure was used in the analyses of pulmonary exacerbations[16]

ADDITIONAL DISCLOSURES FOR THE EXTENSION STUDY

- This study is not included in the approved full Prescribing Information, and the FDA did not consider these data in approving ORKAMBI
- This study may not meet the FDA definition of an adequate and well-controlled study due to its study design

LIMITATIONS OF THE RATE OF CHANGE ANALYSIS

- Rates of clinical trial participation may have affected results
  - Patients who participate in clinical trials may differ systematically from those who do not and could have experienced a reduced rate of decline in lung function relative to those who do not[4]
  - All of the patients treated with ORKAMBI were clinical trial participants[5]
  - 21% of the patients in the matched control group were in a clinical trial in either 2013 or 2014. Some of these patients may have been treated with ORKAMBI in the clinical studies[4]
- Not all variables affecting lung function decline may have been captured in propensity-score matching
  - The analysis is limited to the variables captured in the clinical study and collected in the registry, limiting the ability to match on all reported risk factors for lung function decline[4]

Please see additional limitations and disclosures on the following page.

Limitations and disclosures of the Extension Study and Rate of Change Analysis in patients age 12 years and older (cont)

LIMITATIONS OF THE RATE OF CHANGE ANALYSIS (cont)

- Geographic location of patients may have affected results
  - The CFFPR only includes data from US patients with CF, whereas the ORKAMBI trials included in this analysis were conducted throughout the US, Canada, Europe, and Australia where lung function of the CF populations may differ[4]
- Causality is not definitively established
  - This is not a randomized controlled trial; although the finding of differential rates of lung function decline is likely related to treatment with ORKAMBI, causality cannot be definitively established in the context of this analysis[4]
- Differences in unmeasured characteristics may have affected results
  - Although the propensity-score matching produced a comparison group similar to the ORKAMBI® (lumacaftor/ivacaftor) cohort, there may be differences in unmeasured characteristics[4]
- Patients contributed different amounts of data to the analysis
  - Estimations of average annual rate of decline are based on FEV_1 measurements spanning different lengths of observation for different patients with more patients contributing information about the rate of change in the first year than in the second year[4,8]
- Model assumptions
  - The model assumes that the rate of decline in FEV_1 is constant over the observation period for each individual[4]

ADDITIONAL DISCLOSURES FOR THE RATE OF CHANGE ANALYSIS

- This analysis is not included in the approved full Prescribing Information, and the FDA did not consider this analysis in approving ORKAMBI
- This analysis may not meet the FDA definition of an adequate and well-controlled study due to reliance, in part, on data from a study that was not placebo-controlled

References: 1. ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018. **2.** Wainwright CE, Elborn JS, Ramsey BW, et al. TRAFFIC and TRANSPORT Study Groups. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med.* 2015;373(3):220-231. **3.** A Phase 3 Rollover Study of Lumacaftor in Combination With Ivacaftor in Subjects 12 Years and Older With Cystic Fibrosis. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01931839?term=lumacaftor&rank=9. Updated May 12, 2017. Accessed August 8, 2018. **4.** Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med.* 2017;5(2):107-118. **5.** Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med.* 2017;5(2)(suppl1-28):107-118. **6.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-HQ-20-00239; 2016. **7.** Nicholas J, Guilford MC. Commentary: What is a propensity score? *Br J Gen Pract.* 2008;58(555):687. **8.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-HQ-20-00237; 2016. **9.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-HQ-20-00238; 2016. **10.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-US-02-01559(1); 2016. **11.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-US-20-01588(2); 2016. **12.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-US-02-01558; 2016. **13.** Curran-Everett D, Milgrom H. Post-hoc data analysis: benefits and limitations. *Curr Opin Allergy Clin Immunol.* 2013;13(3):223-224. **14.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-US-02-01051; 2015. **15.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-US-20-01791; 2017. **16.** McColley SA, Konstan MW, Ramsey BW, et al. Association between changes in percent predicted FEV_1 and incidence of pulmonary exacerbations, including those requiring hospitalization and/or IV antibiotics, in patients with CF treatment with lumacaftor in combination with ivacaftor. Poster and abstract presented at: North American Cystic Fibrosis Conference; October 2015; Phoenix, AZ.

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VERTEX

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100/125 mg • 150/188 mg oral granules