ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

CLINICAL DATA AND ANALYSIS

Achieving long-term treatment goals in cystic fibrosis by improving FEV_1, BMI, and pulmonary exacerbations[1-3]

INDICATIONS AND USAGE

ORKAMBI® (lumacaftor/ivacaftor) is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*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.

Please click here for Important Safety Information. Please click here for full Prescribing Information.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

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 in some patients with CF 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. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <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

Please click here for Important Safety Information. Please click here for full Prescribing Information.

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

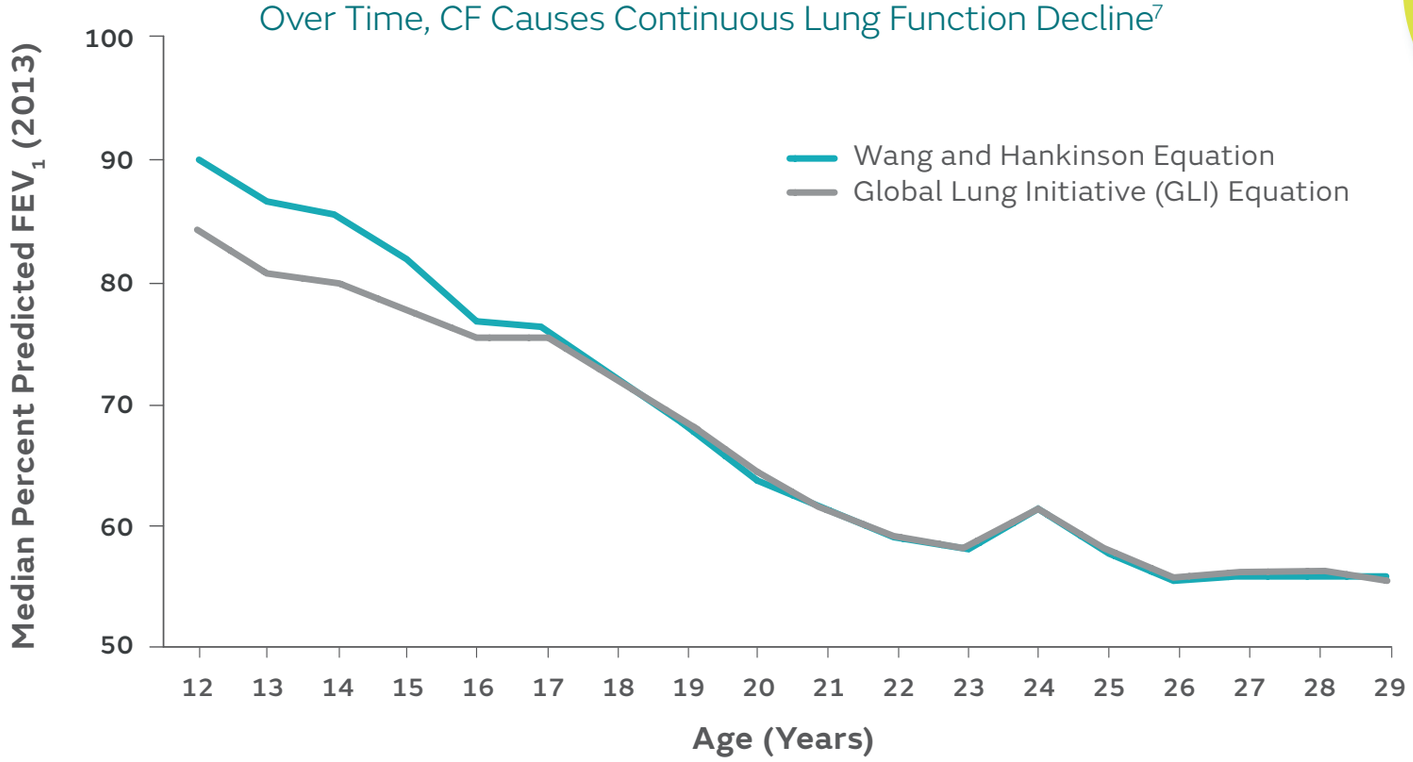
- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients
- 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 for patients age 6 through 11 years in an open-label Phase 3 trial (Trial 3; N=58) was similar to that observed in Trials 1 and 2

Please click here for Important Safety Information. Please click here for full Prescribing Information.

CF CAUSES PROGRESSIVE LUNG DISEASE[4-6]

~1 to 3% Points Annual Decline[8,a]

Over Time, CF Causes Continuous Lung Function Decline[7]



Adapted from Cystic Fibrosis Foundation Patient Registry. *2013 Annual Data Report to the Center Directors*. Bethesda, Maryland. ©2014 Cystic Fibrosis Foundation.

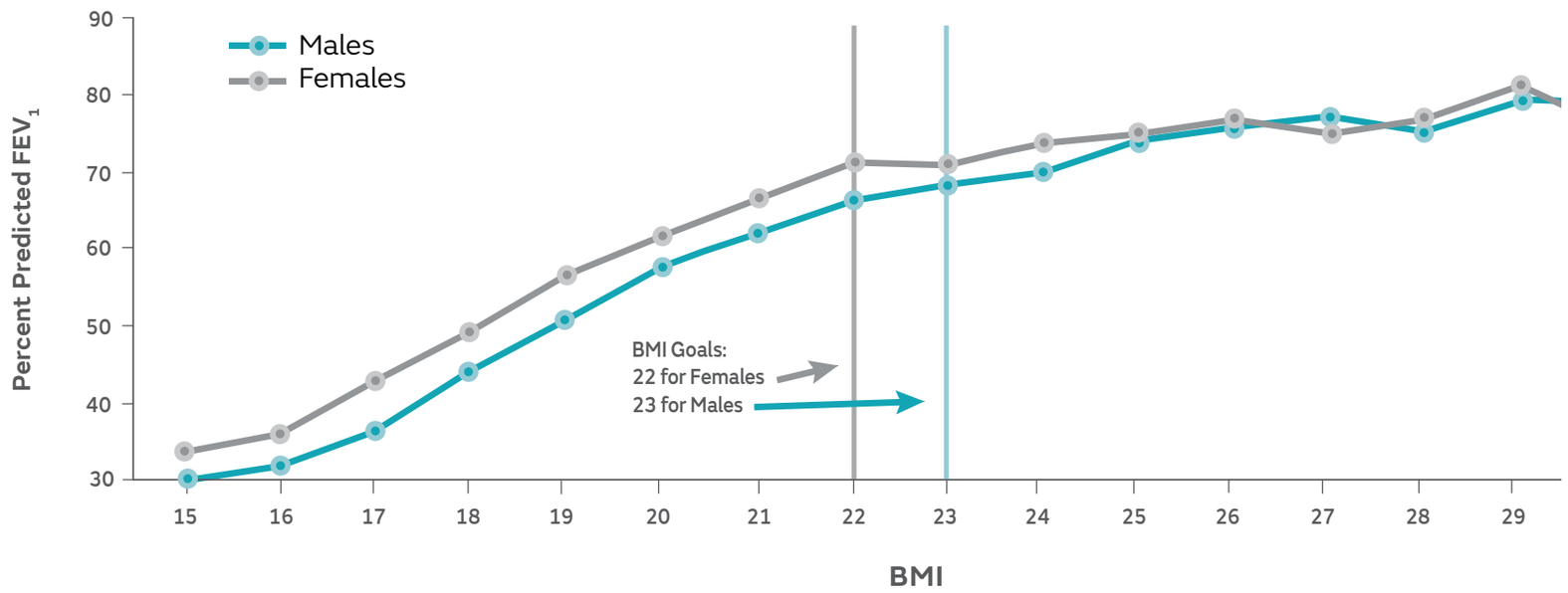
Source of data: Patients with CF treated at CFF-accredited care centers in the US who consented to have their data entered in 2013 in the CFF Registry

[a]Average across the general CF population.

Pulmonary exacerbations may have a negative and lasting impact on lung function[9,10]

POOR WEIGHT GAIN AND LOW BMI ARE CHARACTERISTICS OF CF[11]

Percent Predicted FEV_1 vs BMI Value for Adults Age 20 to 40 Years in 2014[11]



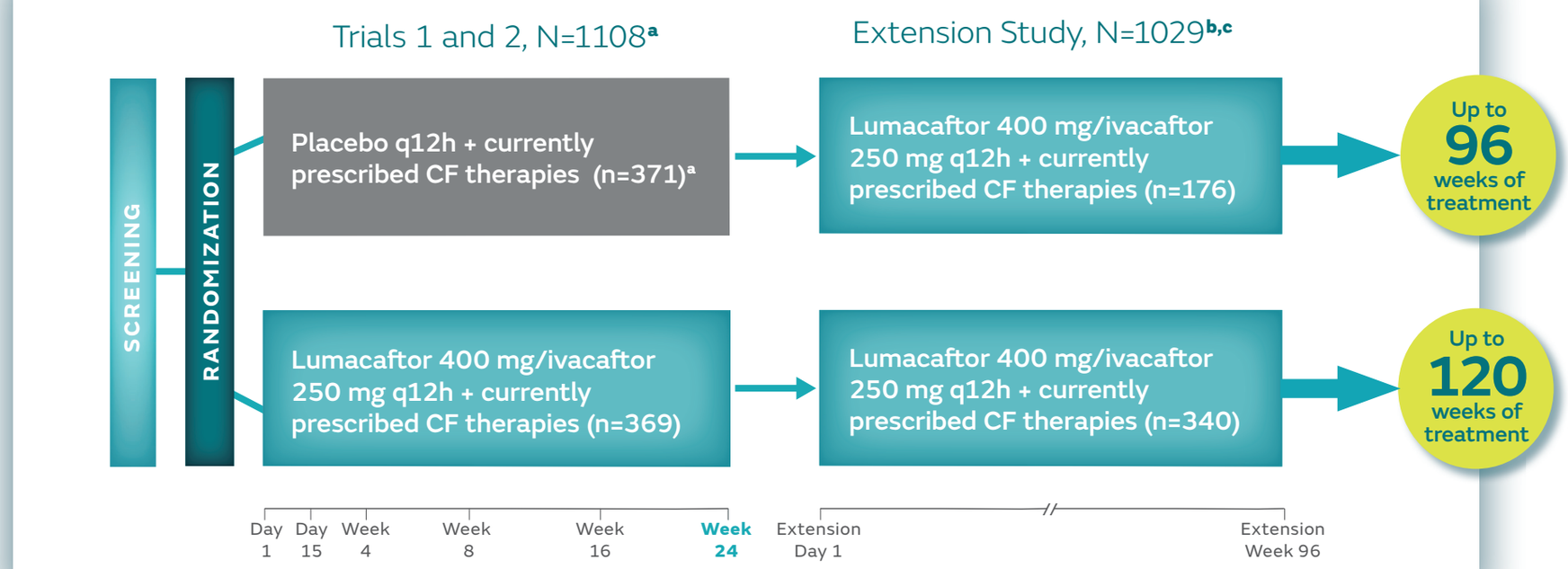
Adapted from Cystic Fibrosis Foundation Patient Registry. 2014 Annual Data Report to the Center Directors. Bethesda, Maryland. ©2015 Cystic Fibrosis Foundation.

BMI, body mass index.

Decreased lung function is associated with reduced nutritional status[11]

DESIGN OF TRIALS AND ANALYSIS

Design of Trials 1 and 2 and Extension Study[1,12,13]



[a]368 received lumacaftor 600 mg qd/ivacaftor 250 mg q12h.[12]

[b]335 continued to receive lumacaftor 600 mg qd/ivacaftor 250 mg q12h, and 178 rolled over from receiving placebo to lumacaftor 600 mg qd/ivacaftor 250 mg q12h.[1]

[c]At the start of the Extension Study, patients who received placebo during Trials 1 and 2 were randomized 1:1 to ORKAMBI (lumacaftor/ivacaftor) or 600 mg lumacaftor/ivacaftor 250 mg q12h.[1]

- Trials 1 and 2 were Phase 3, randomized double-blind, placebo-controlled clinical trials[13]
- Patients who completed Trial 1 and 2 were eligible to enroll in the Extension Study[1]
- The focus of the following data is the approved dose of ORKAMBI lumacaftor 400 mg/ivacaftor 250 mg[1]

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 in some patients with CF 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

DESIGN OF TRIALS AND ANALYSIS (cont)

Trials 1 and 2 pooled analysis:

- The safety of ORKAMBI® (lumacaftor/ivacaftor) was evaluated based on a prespecified pooled analysis[13]
- 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[12]

Key Inclusion and Exclusion Criteria for Trials 1 and 2 and Extension Study[1,12,13]

Key Inclusion Criteria[12]	Key Exclusion Criteria[13]
▪ Confirmed CF diagnosis ▪ Clinically stable ▪ F508del homozygous ▪ ≥12 years of age ▪ Percent predicted FEV1 40 to 90 at screening[a]	▪ 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)

[a]The inclusion criteria at screening was 40 to 90 percent predicted FEV_1. However, in some patients, changes in FEV_1 occurred between screening and baseline (Day 1). In the ORKAMBI (lumacaftor 400 mg/ivacaftor 250 mg) treatment group, baseline percent predicted FEV_1 was <40 in 29 patients (lowest 31.3) and >90 in 3 patients (highest 96.5).[12,13]

AP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase.

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® (lumacaftor/ivacaftor), 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

DESIGN OF TRIALS AND ANALYSIS (cont)

Endpoints for Trials 1 and 2 and Extension Study

	Trials 1 and 2[13]	Extension Study[1]
Primary endpoint	▪ Absolute change from baseline at Week 24 in percent predicted FEV_1, assessed as the average of the treatment effects at Week 16 and 24	▪ Safety of long-term treatment based on adverse events, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard digital electrocardiograms, vital signs, and pulse oximetry
Secondary endpoints ▪ Listed in the order evaluated by the statistical analyses hierarchy of Trials 1 and 2	▪ Relative change from baseline in percent predicted FEV_1, assessed as the average of the treatment effects at Week 16 and Week 24 ▪ Absolute change from baseline at Week 24 in body mass index (BMI) ▪ Absolute change from baseline at Week 24 in the patient-reported Cystic Fibrosis Questionnaire–Revised (CFQ-R) Respiratory Domain score ▪ Proportion of patients with ≥5% relative change from baseline in the percent predicted FEV_1 assessed as the average of the treatment effects at Week 16 and Week 24 ▪ Number of pulmonary exacerbations through Week 24	▪ Absolute change from baseline in percent predicted FEV_1 ▪ Relative change from baseline in percent predicted FEV_1 ▪ Absolute change from baseline in BMI ▪ Number of pulmonary exacerbations starting from previous study ▪ Absolute change from baseline in the CFQ-R Respiratory Domain score[14]

▪ 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[1]

DESIGN OF TRIALS AND ANALYSIS (cont)

Rate of Change Analysis Summary[1]

Objective:

To evaluate whether treatment with ORKAMBI® (lumacaftor/ivacaftor) 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.

Groups compared:

Cohort treated with ORKAMBI from Trials 1 and 2 and Extension Study N=455[a]	**Propensity-score matched control patients homozygous for the *F508del* mutation based on observational data from the US CFFPR N=1588**

- A propensity-score approach was used to match the two groups on known predictors of disease progression
- 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[15]
- Please select the “Rate of Change Appendix” tab below for more information on the Rate of Change Analysis

[a]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.

CFFPR, Cystic Fibrosis Foundation Patient Registry.

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. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

DESIGN OF TRIALS AND ANALYSIS (cont)

ORKAMBI® (lumacaftor/ivacaftor) IMPROVED AND SUSTAINED LUNG FUNCTION AND OTHER KEY CLINICAL OUTCOMES[12,13]

- In each trial, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary end points vs placebo. For an endpoint to be significant, both it and all previous tests had to achieve P≤0.025[13]
  - 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[12, 13]

		Trial 1[12, 13]		Trial 2[12, 13]		Pooled[12]	
		ORKAMBI (n=182)	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 points)[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) *P0*=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 (0.9)	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.[13]
[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 sino-pulmonary 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.

CI, confidence interval.

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 Important Safety Information. Please click here for full Prescribing Information.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

Trials 1 and 2

SAFETY DEMONSTRATED IN TWO PHASE 3 TRIALS[13]

The overall safety profile of ORKAMBI® (lumacaftor/ivacaftor) is based on pooled data

- 2 double-blind, placebo-controlled, Phase 3 clinical trials, each with 24 weeks of treatment (Trials 1 and 2)
- Prespecified pooled analysis
- 1108 patients with CF, age 12 years and older
- Homozygous for the *F508del* mutation in the *CFTR* gene
- Received ≥1 dose of study drug
- 49% female; 99% Caucasian
- 369 received ORKAMBI; 370 received placebo

Discontinuations due to adverse events

- ORKAMBI 5%; placebo 2%

Serious adverse reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, occurring more frequently with ORKAMBI and in ≤1% of patients included pneumonia, hemoptysis, increased blood creatinine phosphokinase, cough, and transaminase elevations

Trials 1 and 2

SAFETY DEMONSTRATED IN TWO PHASE 3 TRIALS[13] (cont)

Adverse Reactions in ≥5% of Patients Treated With ORKAMBI® (lumacaftor/ivacaftor) Ages 12 Years and Older Who Are Homozygous for the *F508del-CFTR* Gene

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.[12]

Trials 1 and 2

SAFETY DEMONSTRATED IN TWO PHASE 3 TRIALS[13] (cont)

Liver-related adverse reactions

- 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 and those who received placebo
- Three patients who received ORKAMBI had liver-related serious adverse reactions, including 2 reported as transaminase elevations and 1 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 6 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® (lumacaftor/ivacaftor) (22%) compared to patients who received placebo (14%)
  - 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 pretreatment FEV_1
- In patients treated with ORKAMBI, the majority of the events began during the first week of treatment
- In patients with reactions occurring within 1 to 2 days after treatment initiation, and who continued treatment, the events usually resolved within the first 2 to 3 weeks of therapy[12]

Menstrual abnormalities

- 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

- 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

Please click here for Important Safety Information. Please click here for full Prescribing Information.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

Extension Study

SAFETY PROFILE AT 96 WEEKS, CONSISTENT WITH TRIALS 1 AND 2[1]

Patient disposition[16]

- 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 of 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[1]

3 deaths occurred across both dose groups; none were considered to be related to the study drug by the study investigators

- 1 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
  - 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 and hemoptysis
  - Serious adverse events occurring at a frequency of 1% to 2% were pneumonia, influenza, respiration abnormal, DIOS, small intestinal obstruction, upper abdominal pain, intestinal obstruction, ALT increase, AST increase, FEV_1 decrease, and CF-related diabetes
- An increase in blood pressure was observed at Week 96
  - 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
  - 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
  - Monitoring of blood pressure is recommended in patients treated with ORKAMBI[1]
- The most frequently (>20%) reported treatment-emergent adverse events were infective pulmonary exacerbation, cough, sputum increased, and hemoptysis, which are all common CF manifestations

Please click here for Important Safety Information. Please click here for full Prescribing Information.

Extension Study

SAFETY PROFILE AT 96 WEEKS, CONSISTENT WITH TRIALS 1 AND 2[1] (cont)

Exposure-Adjusted Adverse Event[a] Profile

	Extension Study	
Event, per 100 Person-Years of Exposure[b]	**Placebo transitioned to ORKAMBI (n=176)**	**ORKAMBI[c] (n=340)**
Infective pulmonary exacerbations of CF	103.5	98.0
Cough	57.3	51.0
Hemoptysis	20.0	26.6
Sputum increased	20.7	20.8
Nasopharyngitis	16.9	19.4
Headache	10.7	14.0
Dyspnea	16.6	12.4
Pyrexia	15.2	11.4
Upper respiratory tract infection	13.1	12.9
Diarrhea	14.5	9.3
Respiration abnormal	12.8	7.7
Nausea	10.4	7.2
Fatigue	9.0	8.4
Abdominal pain	6.6	8.7

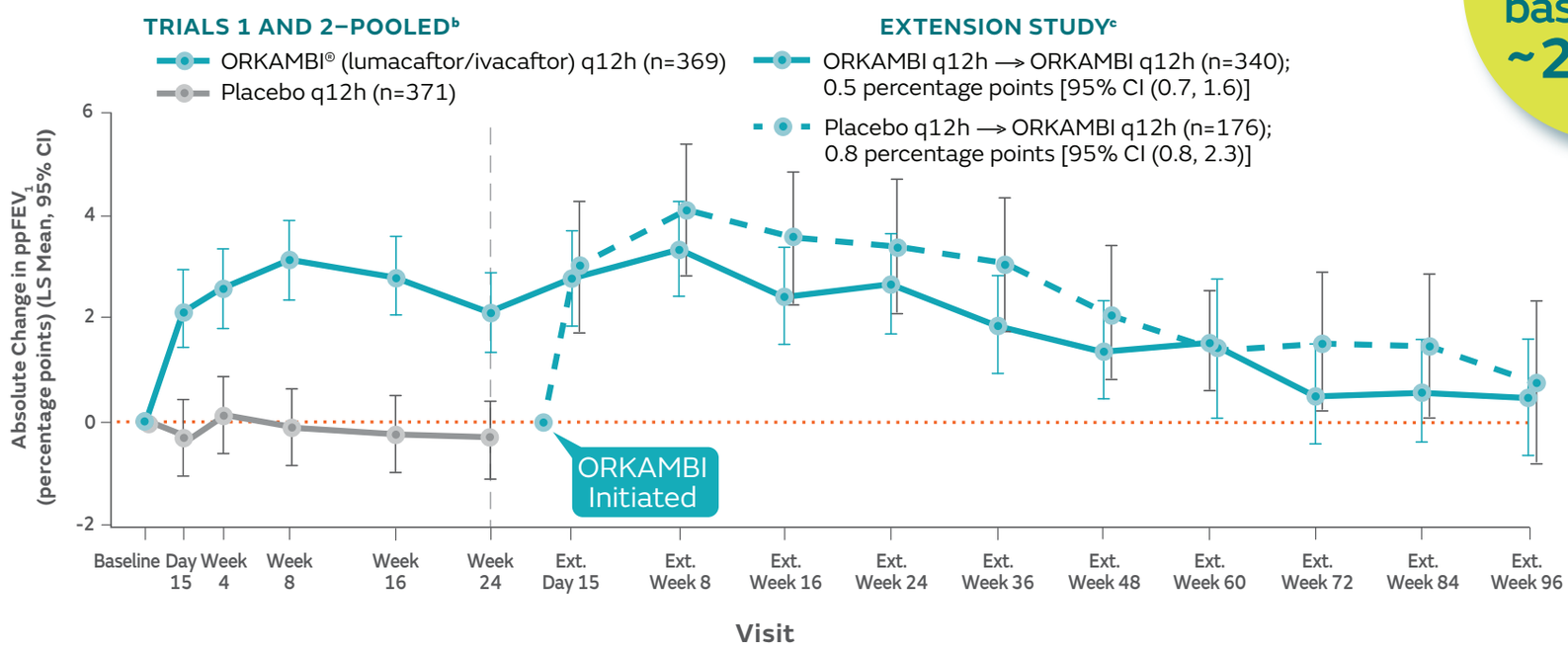
[a]Adverse events with incidence ≥20 events per 100 person-years in any active treatment group are shown.
[b]Number of events per 100 person-years=number of events/total exposure in 100 person-years. One patient with 48 weeks of exposure duration was defined as 1 person-year.
[c]Patients who received ORKAMBI in Trials 1 and 2 had up to 120 weeks of exposure to active treatment.

CF, cystic fibrosis; PEx, pulmonary exacerbation.

Extension Study

FEV_1 MAINTAINED ABOVE BASELINE FOR UP TO 120 WEEKS[1]

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



Mean $ppFEV_1$ above baseline for ~2 years

Adapted from Konstan MW, McKone E, Moss RB, et al. Poster and abstract presented at: 30th Annual North American Cystic Fibrosis Conference, October 2016, Orlando, Florida.

[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.
[c]For the ORKAMBI-to-ORKAMBI group, baseline from Trials 1 and 2 was used. For the placebo-to-ORKAMBI group, baseline from treatment initiation in the Extension Study was used.

View Limitations

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

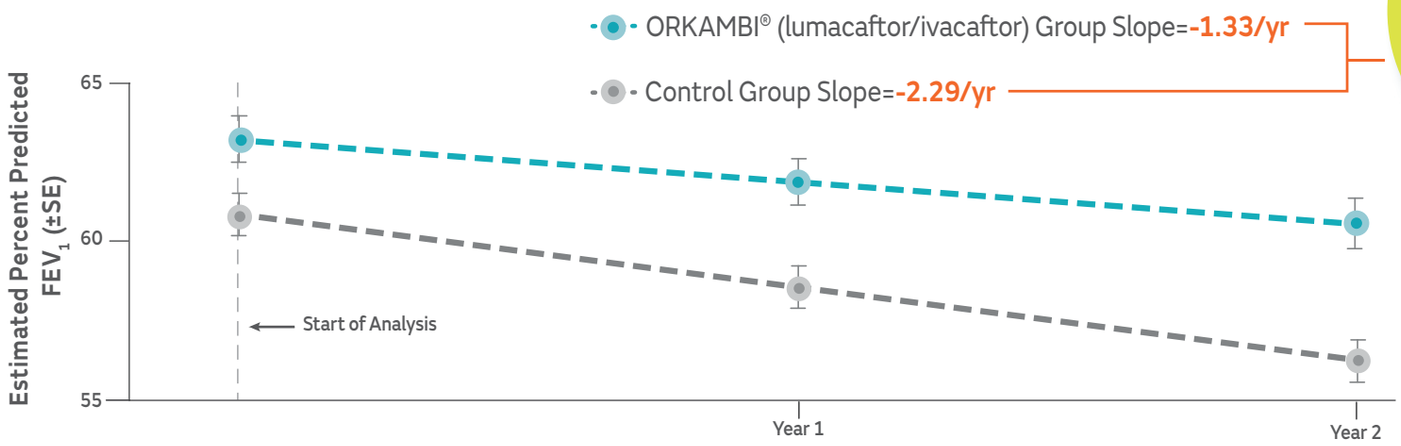
Please click here for Important Safety Information. Please click here for full Prescribing Information.

Rate of Change Analysis

REDUCED RATE OF LUNG FUNCTION DECLINE vs MATCHED CONTROLS[1]

Analysis suggests ORKAMBI® (lumacfator/ivacaftor) modifies the course of CF

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



42%
reduction in rate of decline (*P*<0.001)

Adapted from Konstan MW, McKone E, Moss RB, et al. Poster and abstract presented at: 30th Annual North American Cystic Fibrosis Conference, October 2016, Orlando, Florida.

[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.

View Limitations

- Patients contributed the following amount of data:[17]
  - 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

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 for patients age 6 through 11 years in an open-label Phase 3 trial (Trial 3; N=58) was similar to that observed in Trials 1 and 2

Please click here for Important Safety Information. Please click here for full Prescribing Information.

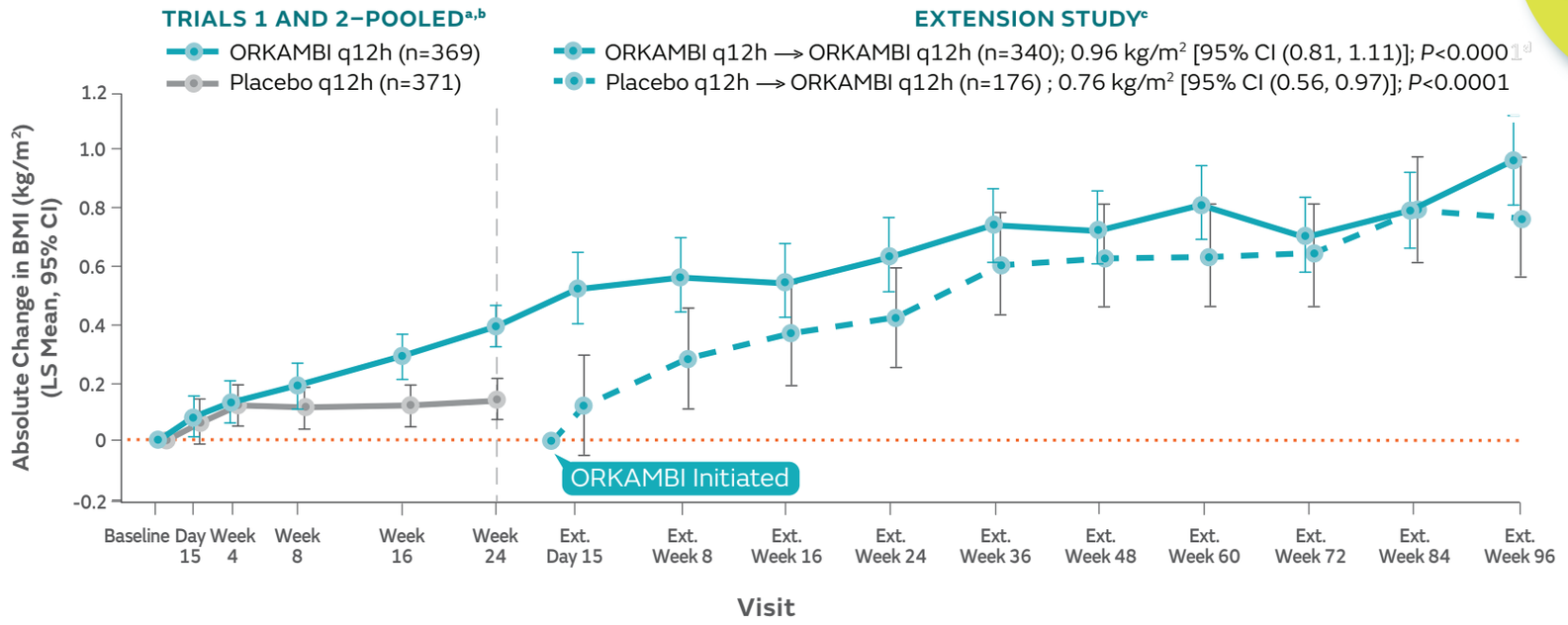
Extension Study

BMI IMPROVEMENTS SUSTAINED FOR UP TO 120 WEEKS[1]

Ongoing increases in mean BMI were seen in both ORKAMBI® (lumacaftor/ivacaftor) treatment groups

BMI increased over time

Mean Absolute Change in BMI in Patients Who Rolled Over From Trials 1 and 2 to the Extension Study



Adapted from Konstan MW, McKone E, Moss RB, et al. Poster and abstract presented at: 30th Annual North American Cystic Fibrosis Conference, October 2016, Orlando, Florida.

[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.

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

[c]For the ORKAMBI-to-ORKAMBI group, baseline from Trials 1 and 2 was used. For the placebo-to-ORKAMBI group, baseline from treatment initiation in the Extension Study was used.

[d]Includes data from Trials 1 and 2.

View Limitations

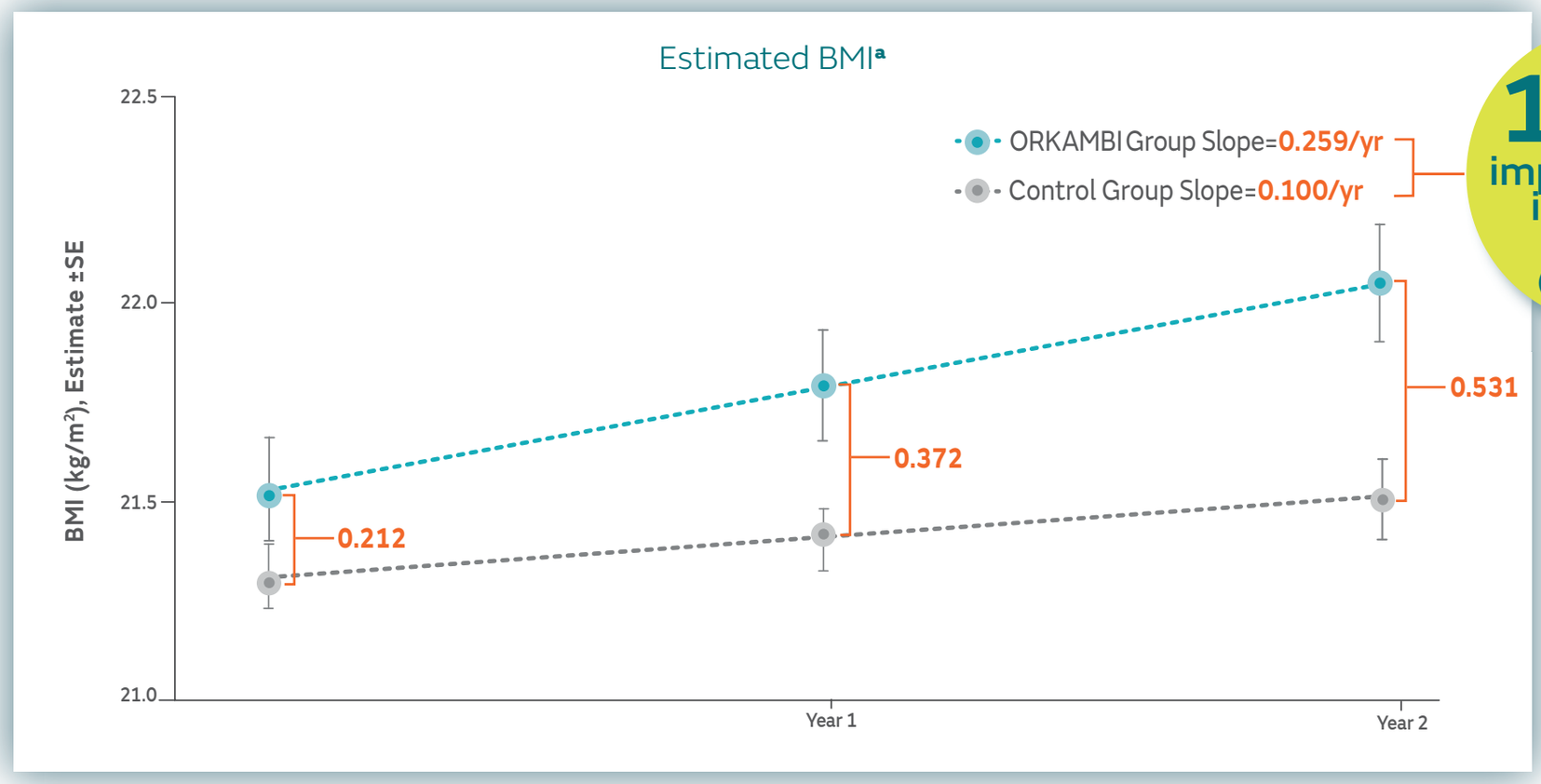
IMPORTANT SAFETY INFORMATION

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

Rate of Change Analysis

INCREASING IMPROVEMENT IN BMI RATE OF CHANGE VS MATCHED CONTROLS[1]



160% improvement in rate of change (*P*=0.002)

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

View Limitations

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 in some patients with CF 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

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

Extension Study

Improvements in CFQ-R

CFQ-R increased in both treatment groups[14]

- At Week 96 of the Extension Study, the LS mean absolute change from baseline in CFQ-R Respiratory Domain 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[a]

[a]For the ORKAMBI-to-ORKAMBI group, baseline from Trials 1 and 2 was used. For the placebo-to-ORKAMBI group, baseline from treatment initiation in the Extension Study was used.

CFQ-R, Cystic Fibrosis Questionnaire-Revised.

IMPORTANT SAFETY INFORMATION

Liver-related Events

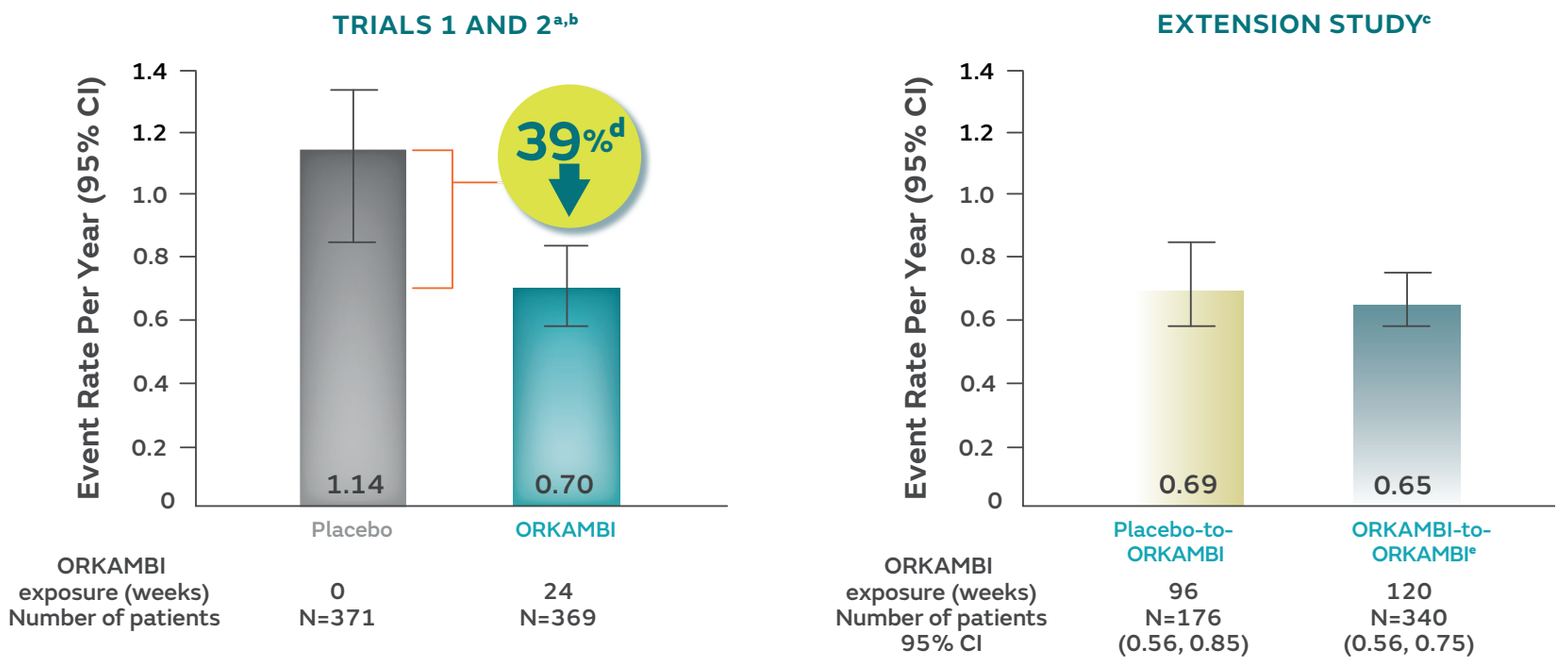
- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating 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

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

Extension Study

REDUCTION IN PULMONARY EXACERBATIONS MAINTAINED UP TO 120 WEEKS[1,18]

Annualized Pulmonary Exacerbation Rate



[a] Adapted from Konstan MW, McKone E, Moss RB, et al. Poster and abstract presented at: 30th Annual North American Cystic Fibrosis Conference, October 2016, Orlando, Florida.

[b] 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.

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

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

[e] For the ORKAMBI-to-ORKAMBI group, baseline from Trials 1 and 2 was used. For the placebo-to-ORKAMBI group, baseline from treatment initiation in the Extension Study was used.[1]

[f] Compared to placebo at Week 24.

[g] Includes data from Trials 1 and 2.

View Limitations

IMPORTANT SAFETY INFORMATION

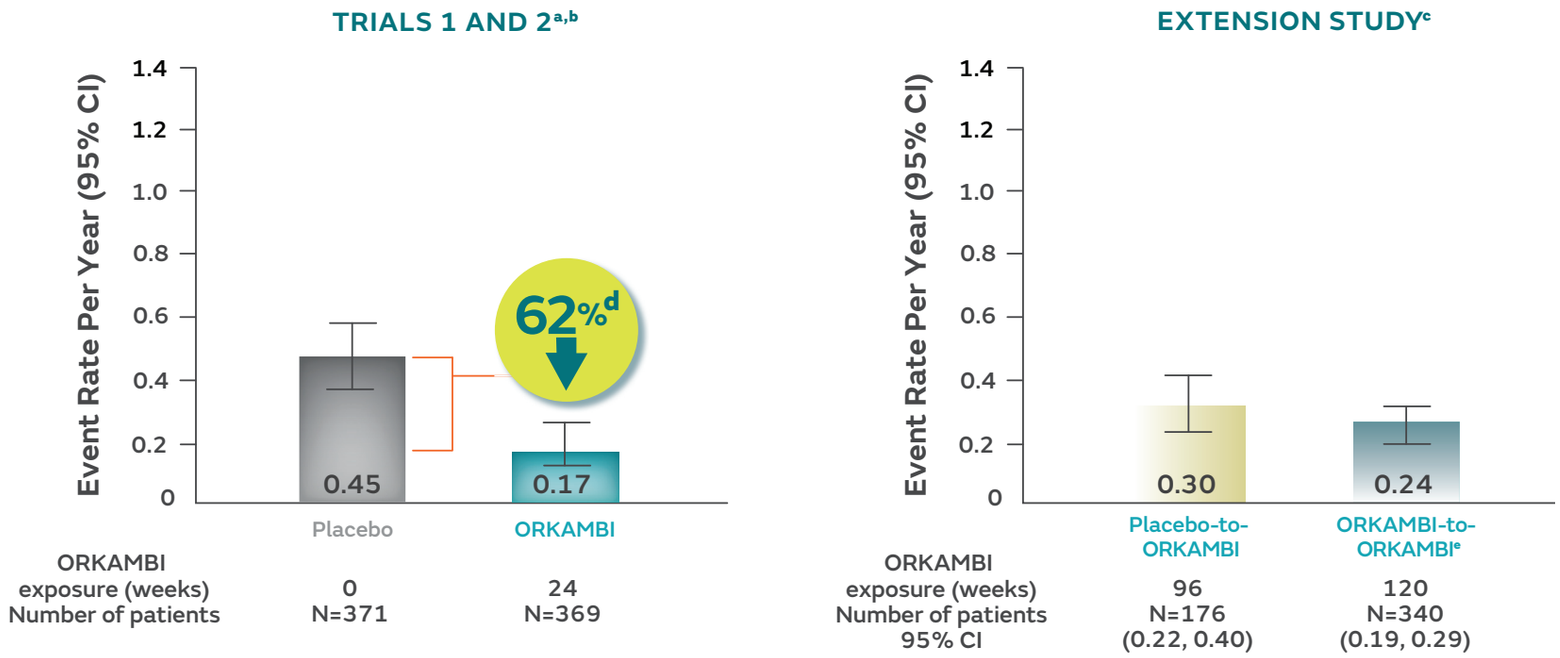
Respiratory Events

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI® (lumacaftor/ivacaftor) compared to those who received placebo. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

Extension Study

REDUCTION IN PULMONARY EXACERBATIONS REQUIRING HOSPITALIZATION MAINTAINED UP TO 120 WEEKS[1,19]

Annualized Rate of Pulmonary Exacerbations Requiring Hospitalization



[a] Adapted from Konstan MW, McKone EF, Moss RB, et al. Poster and abstract presented at: 30th Annual North American Cystic Fibrosis Conference, October 2016, Orlando, Florida.

[b] 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.

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

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

[e] For the ORKAMBI-to-ORKAMBI group, baseline from Trials 1 and 2 was used. For the placebo-to-ORKAMBI group, baseline from treatment initiation in the Extension Study was used.[1]

[f] Compared to placebo at Week 24.

[g] Includes data from Trials 1 and 2.

View Limitations

- These results are based on a post hoc analysis. This analysis does not ascertain whether findings were attributable to ORKAMBI® (lumacaftor/ivacaftor)

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

Please click here for Important Safety Information. Please click here for full Prescribing Information.

LIMITATIONS AND DISCLOSURES

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[20]
- The Extension Study was not a placebo-controlled study[20]
- All patients in the Extension Study knew they were on active drug, which may have introduced bias related to awareness of treatment[20]
- Trials 1 and 2 required patients to remain on their usual prescribed CF regimen.[13] In the Extension Study, patients may have had changes in their stable medication regimen,[20] 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)
- Although a relatively large study over a 96-week period, rare adverse events might not have been detected

LIMITATIONS AND DISCLOSURES (cont)

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[21]
  - All of the patients treated with ORKAMBI® (lumacaftor/ivacaftor) were clinical trial participants[22]
  - 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[23]
- 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[24]
- 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[11, 12]
- 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[22]
- Differences in unmeasured characteristics may have affected results
  - Although the propensity-score matching produced a comparison group similar to the ORKAMBI cohort, there may be differences in unmeasured characteristics[24]
- Patients contributed different amounts of data to the analysis[17]
  - 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
- Model assumptions[22]
  - The model assumes that the rate of decline in FEV_1 is constant over the observation period for each individual

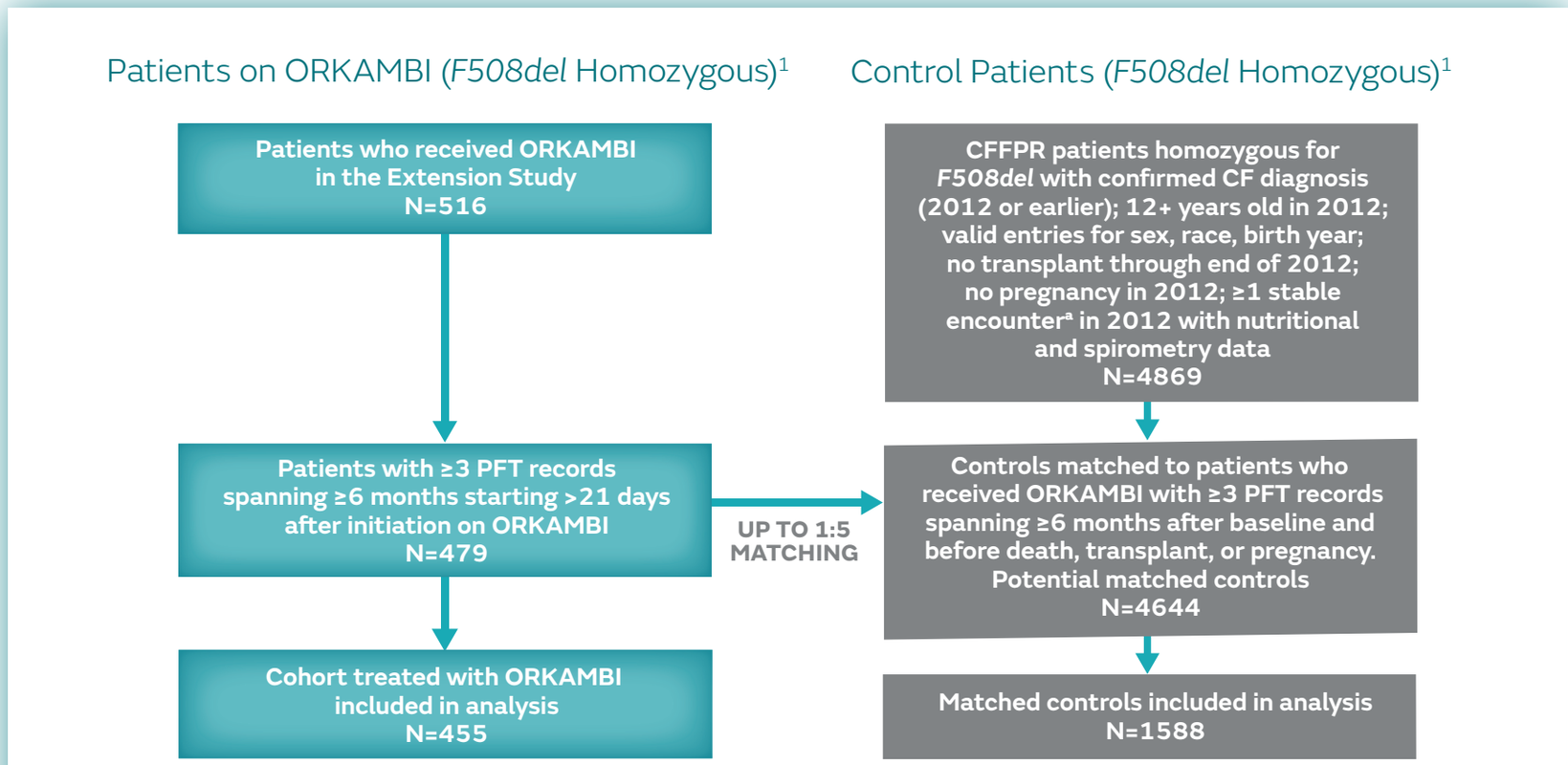
Additional disclosures

- 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

Rate of Change Analysis

OBJECTIVE AND DESIGN[1]

- The objective of this analysis was to evaluate whether treatment with ORKAMBI® (lumacaftor/ivacaftor) affects the rate of change in pulmonary function in patients 12 years and older who are homozygous for the *F508del* mutation
- This analysis utilized data from 455 patients treated with ORKAMBI from Trials 1, 2, and the Extension Study. A matched cohort of 1588 patients from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) was used as the comparator because there was no placebo group in the Extension Study



[a]Stable encounter defined as no material change in lung function or routine medication from prior encounter and no evidence of a care episode.[3]

PFT, pulmonary function test.

- 24 ORKAMBI patients 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

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 Important Safety Information. Please click here for full Prescribing Information.

Rate of Change Analysis

PATIENT MATCHING AND SELECTION

- A propensity score approach was used to match the two groups on known predictors of disease progression[1,25]
- 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[15]

Propensity Scores Were Based on Identified Risk Factors for FEV_1 Decline:

- **$ppFEV_1$, $ppFEV_1$ decile, ppFVC, $ppFEV_1$/ppFVC ratio, $ppFEF_{25-75}$**
- **Age, sex**
- **BMI, weight *z*-score, height *z*-score**
- **Bacteriology**
  - *Pseudomonas aeruginosa, Burkholderia species,* MRSA, MSSA, *Aspergillus, Stenotrophomonas, Alcaligenes*
- **CF-related diabetes**
- **Antibiotics**
  - Inhaled tobramycin
  - Colistin
  - Inhaled aztreonam
- **Other therapies**
  - Dornase alfa
  - Antifungals
  - Acetylcysteine
  - Leukotriene modifiers

FEF_{25-75}, forced expiratory flow in the mid-expiratory range; FVC, forced vital capacity; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

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

Please click here for Important Safety Information. Please click here for full Prescribing Information.

Rate of Change Analysis

PATIENT MATCHING AND SELECTION (cont)

- A propensity score approach was used to match the two groups on known predictors of disease progression[1,25]
- 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[15]

Select Patient Characteristics for ORKAMBI® (lumacaftor/ivacaftor) and Control Groups[26]

		ORKAMBI (N=455)	Control (N=1588)	*P* Value
Demographics	Female, n (%)	216 (47.5)	745 (46.9)	0.84
	Age, year, mean (±SD)	25.75 (9.56)	25.17 (9.27)	0.18
Nutritional status	BMI, mean (±SD)	21.28 (2.94)	21.31 (3.12)	0.95
	BMI *z*-score, mean (±SD)	-0.32 (0.90)	-0.30 (0.93)	0.84
Pulmonary status	FEV_1, percentage points, mean (±SD)[a]	59.84 (13.83)	61.75 (16.32)	0.37
Bacteriology	*Pseudomonas* positive, n (%)	343 (75.4)	1178 (74.2)	0.62
	MRSA, n (%)	101 (22.2)	452 (28.5)	0.013
	MSSA, n (%)	183 (40.2)	731 (46.0)	0.052
Therapies	Dornase alfa, n (%)	340 (74.7)	1277 (80.4)	0.026
	Tobramycin, inhaled, n (%)	139 (30.5)	594 (37.4)	0.031

[a]Rate of decline analysis utilized GLI equations to calculate percent predicted FEV_1.

GLI, Global Lung Initiative equation.

- The shaded boxes in the table indicate statistically significant differences that were seen in 3 of the patient characteristics
  - Sensitivity analyses controlling for known differences at baseline produced similar results

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 in some patients with CF 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 Important Safety Information. Please click here for full Prescribing Information.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

In patients age 12 years and older homozygous for the *F508del-CFTR* mutation

Achieving long-term treatment goals in cystic fibrosis[1-3]

LUNG FUNCTION[1,12]

+2.8 percentage points — Absolute change in FEV_1 vs placebo in Trials 1 and 2 (pooled)

~2 years — FEV_1 maintained above baseline in the Extension Study

42% — Reduction in the rate of FEV_1 decline in the Rate of Change Analysis

BODY MASS INDEX (BMI)[1,12]

+0.24 kg/m^2 — Change in BMI vs placebo in Trials 1 and 2 (pooled)

~2 years — BMI improvements maintained in the Extension Study

160% — BMI improvements in Rate of Change Analysis

PULMONARY EXACERBATIONS[12,19*]

39% — Reduction in rate of pulmonary exacerbations vs placebo in Trials 1 and 2 (pooled)

62% — Reduction in rate of pulmonary exacerbations requiring hospitalizations vs placebo in Trials 1 and 2 (pooled)

*Compared with placebo at Week 24.
†There is no formal definition of disease modification

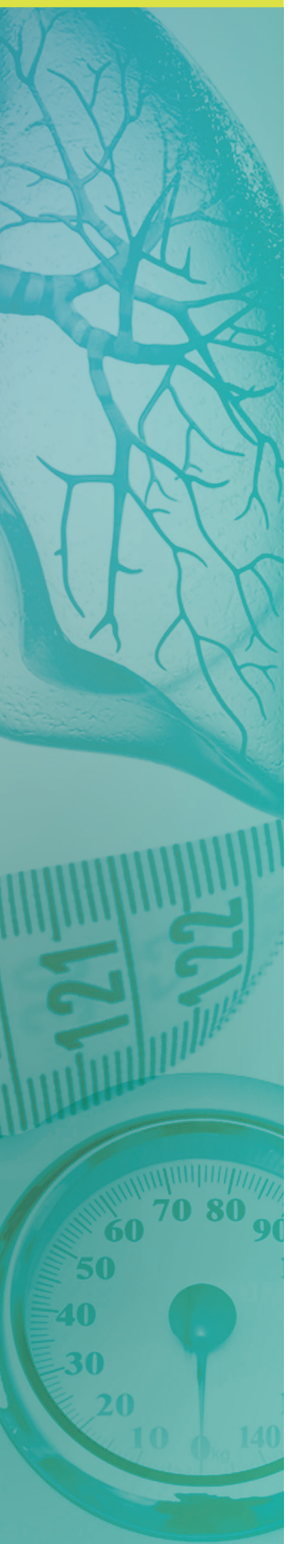
Data suggest ORKAMBI modifies the course of CF†

SAFETY[1,13]

>1100 — Patients studied in Trials 1 and 2. 1029 patients studied in the Extension Study.

- 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 Trials 1 and 2 occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a higher rate than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza
- Safety profile at 96 weeks consistent with Trials 1 and 2

Please click here for Important Safety Information. Please click here for full Prescribing Information.



ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

For more information, visit www.ORKAMBIhcp.com

References: 1. Konstan MW, McKone E, Moss R, et al. Evidence of reduction in annual rate of FEV_1 decline and sustained benefits with lumacaftor and ivacaftor in patients with cystic fibrosis homozygous for *F508del-CFTR*. Poster and abstract presented at: 30th Annual North American Cystic Fibrosis Conference; October 27-29, 2016; Orlando, Florida. **2.** Mogayzel PJ et al. Cystic Fibrosis Pulmonary Guidelines Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2013;187(7):680-689. **3.** Stallings VA, Stark LJ, Robinson KA et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc*. 2008;108:832-839. **4.** Welsh MJ, Ramsey BW, Accurso F, Cutting GR. Cystic fibrosis: membrane transport disorders. In: Valle D, Beaudet A, Vogelstein B, et al, eds. The Online Metabolic & Molecular Bases of Inherited Disease. The McGraw-Hill Companies Inc; 2004: part 21, chap 201. www.ommbid.com. **5.** Mall MA, Elborn JS, eds. Cystic Fibrosis. Wakefield, UK: European Respiratory Society; 2014. **6.** Cystic Fibrosis Foundation. https://www.cff.org/About-Us/Media-Center/Media-FAQs. Updated July 13, 2015. Accessed August 16, 2016. **7.** Cystic Fibrosis Foundation Patient Registry. 2013 Annual Data Report to the Center Directors. Bethesda, Maryland. © 2014 Cystic Fibrosis Foundation. **8.** Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros*. 2010;9(4):250-256. **9.** Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J*. 2012;40(1):61-66. **10.** Sanders DB, Bittner RCL, Rosenfeld M, et al. Failure to recover baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med*. 2010;182(5):627-632. **11**. Cystic Fibrosis Foundation Patient Registry. 2014 Annual Data Report. Bethesda, Maryland. ©2015 Cystic Fibrosis Foundation. **12.** 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. **13.** ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; September 2016. **14.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-00234. 2016 **15.** Nicholas J, Guilford MC. Commentary: What is a propensity score? Br J Gen Pract. 2008;58(555):687. **16.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-02-01559(1). 2016. **17.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-00237. 2016. **18.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-00235. 2016 **19**. Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-00236. 2016 **20.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-02-01576(1). 2016 **21**. Goss CH, Rubenfeld GD, Ramsey BW, Aitken ML. Clinical trial participants compared with nonparticipants in cystic fibrosis. *Am J Repir Crit Care Med*. **22.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-02-01600; 2016. **23.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-01596; 2016. **24.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-01577; 2016. **25.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-HQ-02-00025; 2016. **26.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-US-20-00233; 2016.

VERTEX®

Please click here for Important Safety Information. Please click here for full Prescribing Information.