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

An overview of long-term safety data in patients taking ORKAMBI age 2 through 5 years who are homozygous for the *F508del-CFTR* mutation[1-3]

Patients with cystic fibrosis (CF) shown throughout this brochure may or may not currently be on ORKAMBI.

INDICATIONS AND USAGE

ORKAMBI® (lumacaftor/ivacaftor) is a combination of lumacaftor and ivacaftor indicated for the treatment of 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.

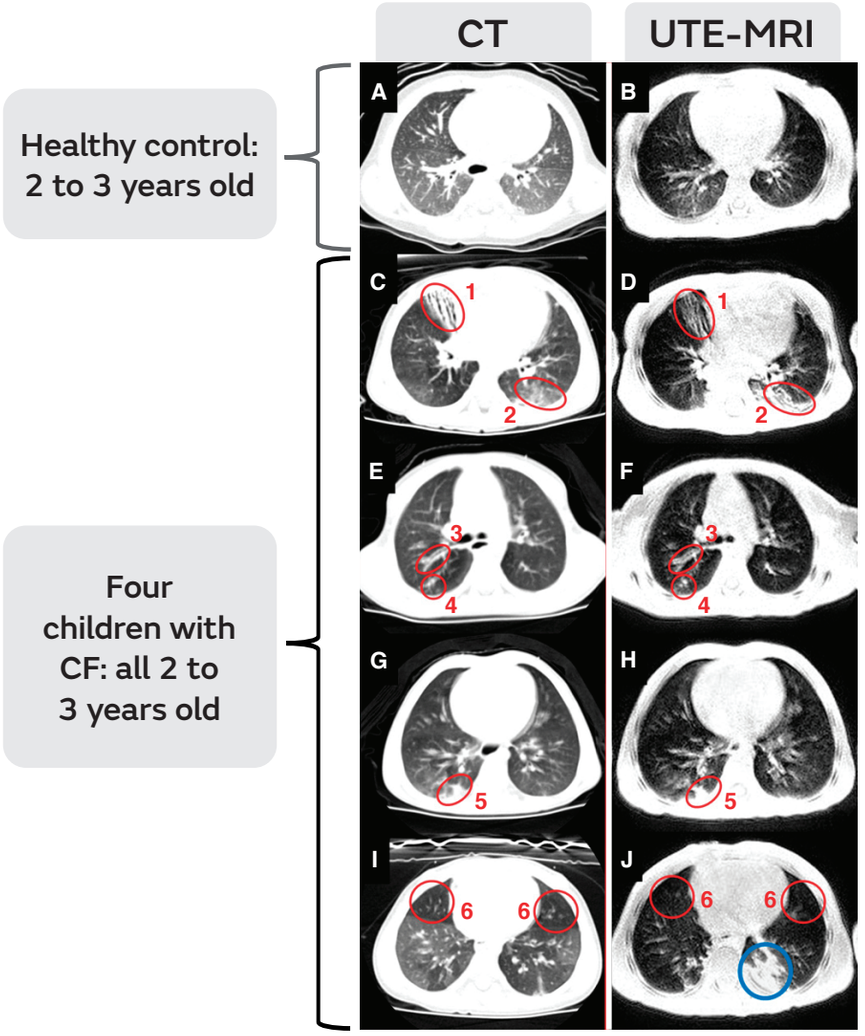
CFTR, cystic fibrosis transmembrane conductance regulator.

Please click for Important Safety Information and full Prescribing Information for ORKAMBI.

Structural lung damage has been observed in patients with CF as young as 33 months[4]

EVIDENCE SUGGESTS STRUCTURAL LUNG DAMAGE IN CF BEGINS AT A YOUNG AGE, IS PROGRESSIVE, AND REDUCES QUALITY OF LIFE[5]

- A study indicates that there is an increasing prevalence of structural lung disease early in life, most notably bronchiectasis and mucus plugging[5]
- Prevalence of bronchiectasis increases to 73.7% at age 5 to 6 years[5]
- Mucus plugging increases to 37.1% at age 5 to 6 years[5]
- These abnormalities are predictive of BMI-for-age z-score declines[5]



- The top left and right scans (CT and UTE-MRI) show a healthy (without CF) patient with normal chest findings[4]
- The subsequent scans underneath show 4 patients with CF, which visualize:
  1. bronchiectasis[4]
  2. ground-glass opacity[4]
  3. bronchial wall thickening[4]
  4. mucus plugging[4]
  5. consolidation[4]
  6. air trapping[4]

(A) CT image of an age-matched healthy patient with normal chest findings. (B) UTE-MRI of an aged-matched healthy patient. (C–J) CT images (left) and matched UTE-MRI scans (right) of four patients with CF aged 33 to 47 months old. The blue circle captures the accumulated anesthesia induced-atelectasis.[4]

CT, computed tomography; UTE-MRI, ultrashort echo-time magnetic resonance imaging.

References: 4. Roach DJ, Crémillieux Y, Fleck RJ, et al. Ultrashort echo-time magnetic response imaging is a sensitive method for the evaluation of early cystic fibrosis lung disease. *Ann Am Thorac Soc.* 2016;13(11):1923-1931. **5.** Turovic L, Caudri D, Rosenow T, et al. Structural determinants of long-term functional outcomes in young children with cystic fibrosis. *Eur Respir J.* 2020;55(5):1900748.

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

ALT, alanine aminotransaminase; AST, aspartate aminotransaminase.

Please click for full Prescribing Information for ORKAMBI.

Important Safety Information (cont'd)

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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A long-term safety study in patients with CF age 2 through 5 years[1-3]

TRIAL 6 | PHASE 3, OPEN-LABEL SAFETY STUDY[1,2,6] **EXTENSION STUDY | OPEN-LABEL EXTENSION STUDY OF TRIAL 6**[3]

lumacaftor 100 mg/ivacaftor 125 mg q12h granules (<14 kg) or lumacaftor 150 mg/ivacaftor 188 mg q12h granules (≥14 kg)

SELECTED INCLUSION CRITERIA[2,6,b]

- Confirmed CF diagnosis, homozygous for the *F508del* mutation, clinically stable, age 2 through 5 years
- Body weight ≥8 kg at screening

PRIMARY ENDPOINT[2]

- Safety and tolerability up to Week 24, including assessments of adverse events and clinical laboratory values*

SELECTED SECONDARY ENDPOINTS[2]

- Absolute change from baseline to Week 24 for sweat chloride concentration,[c] BMI, and BMI-for-age z-score

SELECTED INCLUSION CRITERIA[3,7,d]

- Completed 24 weeks of ORKAMBI treatment and the safety follow-up in Trial 6
- Willingness to remain on a stable CF medication regimen through safety follow-up visit in the Extension Study

PRIMARY ENDPOINT[3]

- Safety and tolerability up to Week 96, including assessments of adverse events and clinical laboratory values*

SELECTED SECONDARY ENDPOINTS[3]

- Absolute change from baseline at 96 weeks for sweat chloride level, BMI, and BMI-for-age z-score

*Additional assessments within the primary endpoint were also studied.

[a]Patients remained on currently prescribed CF therapies (including during the washout).[6]

[b]Selected exclusion criteria included hemoglobin <10 g/dL; ALT, AST, or total bilirubin >2 x ULN; abnormal renal function; acute upper- or lower-respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1; and history of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant.[6]

[c]Assessed at Week 24 and at Week 26 (after the washout).[1,2]

[d]Selected exclusion criteria included having prematurely discontinued lumacaftor/ivacaftor treatment in Trial 6; history of drug intolerance or other serious reactions to lumacaftor/ivacaftor in Trial 6 that would pose an additional risk to the patient in the opinion of the investigator; an abnormality in liver test results at the completion of Trial 6 meeting the criteria for interruption of lumacaftor/ivacaftor at the completion of Trial 6 and for which no convincing alternative etiology is identified.[7]

BMI, body mass index; q12h, every 12 hours; ULN, upper limit of normal.

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Selected baseline characteristics[2,3]

	TRIAL 6		EXTENSION STUDY
	ORKAMBI® (LUMACAFTOR 100 mg/ IVACAFTOR 125 mg q12h) N=19 (SD)	ORKAMBI (LUMACAFTOR 150 mg/ IVACAFTOR 188 mg q12h) N=41 (SD)	ORKAMBI N=57 (SD)
Mean age, months	31.6 (5.1)	49.9 (10.6)	43.2 (12.2)
SwCl, mmol/L	105.5 (8.0)	106.0 (7.2)	105.8 (7.3)
BMI, kg/m^2	16.0 (1.1)	16.0 (1.0)	15.99 (1.05)
BMI-for-age z-score	-0.10 (0.85)	0.30 (0.76)	0.16 (0.82)

SD, standard deviation; SwCl, sweat chloride

TRIAL 6 AND EXTENSION STUDY LIMITATIONS[2,3]

- The study was open label and not placebo controlled; therefore, causality cannot be attributed
- All patients in the study knew they were on active drug, which may have introduced bias related to awareness of treatment

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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Long-term safety results in patients with CF age 2 through 5 years[1-3]

Liver-related adverse events[1,7]

	TRIAL 6 N=60 (%)	EXTENSION STUDY N=57 (%)
ELEVATED ALT OR AST	ORKAMBI® (LUMACAFTOR/IVACAFTOR)	ORKAMBI
>3 x ULN	9 (15.0)	11 (19.3)
>5 x ULN	7 (11.7)	6 (10.5)
>8 x ULN	5 (8.3)	2 (3.5)

- In Trial 6, 3 patients discontinued ORKAMBI treatment permanently due to transaminase elevations[1]
- In both Trial 6 and the Extension Study, no patients had total bilirubin levels >2 x ULN[1,3]

DISCONTINUATIONS AND SERIOUS ADVERSE EVENTS

TRIAL 6

- 3 patients (5%) discontinued due to adverse events (3 with transaminase elevations)[1,2]
- 4 patients (7%) experienced serious adverse events (1 with viral gastroenteritis, 1 with constipation, and 2 with infective pulmonary exacerbations of CF)[2]

EXTENSION STUDY

- 3 patients (5%) discontinued due to adverse events (1 with viral gastritis and metabolic acidosis, 1 with pancreatitis and elevations in transaminases, and 1 with elevations in transaminases)[3]
- Serious adverse events occurred in 15 patients (26%); those that occurred in ≥3% of patients included infective pulmonary exacerbations of CF (n=6 [11%]) and pneumonia (n=2 [4%])[3]

Please click here to see the study limitations for Trial 6 and the Extension Study.

ULN, upper limit of normal.

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Overview of safety results from Trial 6 and the Extension Study

Respiratory-related adverse events[3,6]

	TRIAL 6 N=60 (%)	EXTENSION STUDY N=57 (%)
ADVERSE EVENT (preferred term)	**ORKAMBI® (LUMACAFTOR/IVACAFTOR)**	**ORKAMBI**
Dyspnea	3 (5.0)	3 (5.0)
Wheezing	3 (5.0)	3 (5.0)
Respiration abnormal	1 (2.0)	1 (2.0)

TRIAL 6

- No respiratory events led to treatment interruption or discontinuation[2]

EXTENSION STUDY

- No respiratory events led to treatment interruption or discontinuation[3]

Please click here to see the study limitations for Trial 6 and the Extension Study.

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

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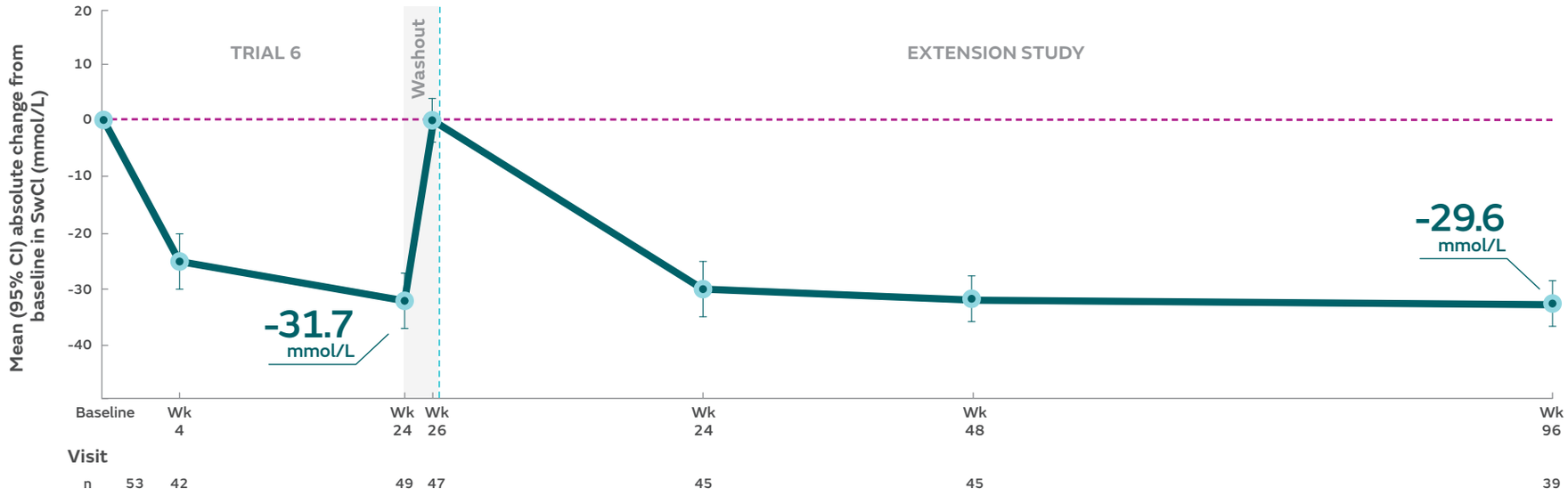
Sweat chloride results[1-3]

Secondary endpoint: absolute change from baseline in sweat chloride



MEAN ABSOLUTE WITHIN-GROUP CHANGE IN SWEAT CHLORIDE

TRIAL 6

- From baseline at Week 24 (n=49): -31.7 mmol/L (95% CI -35.7, -27.6) reduction[1,2]
- After washout, from Week 24 to Week 26 (n=47): +33.0 mmol/L (95% CI 28.9, 37.1)[1,2]

EXTENSION STUDY

- From Trial 6 baseline to Week 96: -29.6 mmol/L (95% CI -33.7, -25.5) reduction[3]

There was no direct correlation between decrease in sweat chloride level and improvement in lung function ($ppFEV_1$).[1]

Please click here to see the study limitations for Trial 6 and the Extension Study.

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. 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

CI, confidence interval; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; Wk, week.

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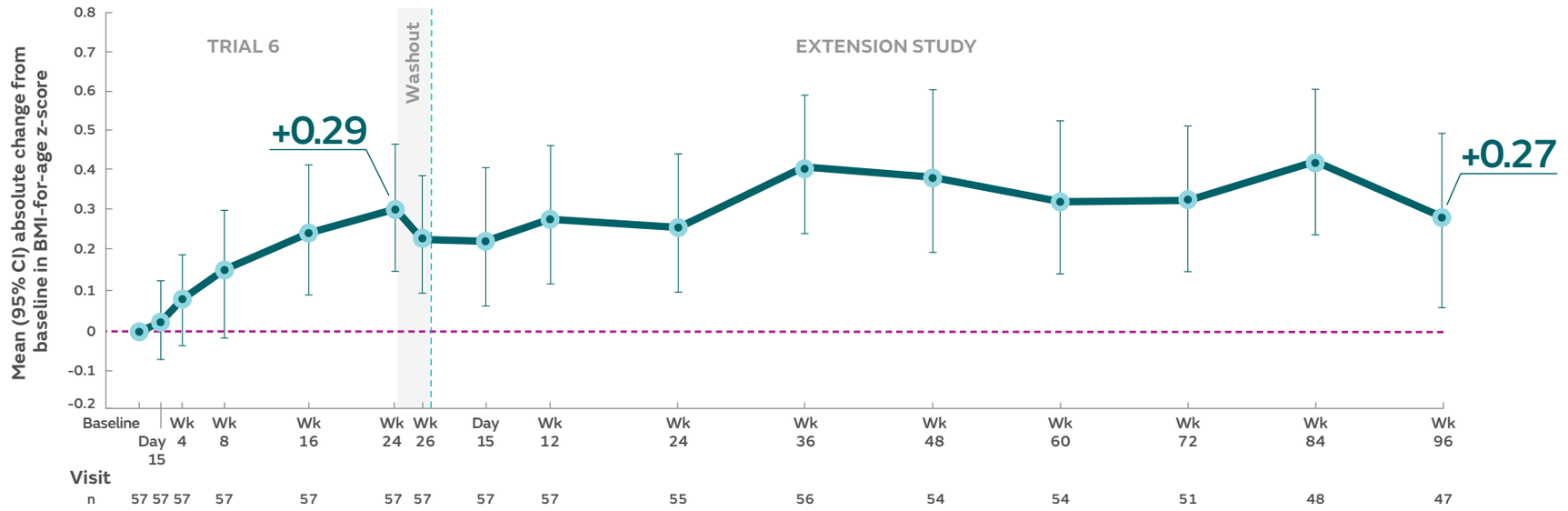
BMI-for-age z-score results[2,3]

Secondary endpoint: absolute change from baseline in BMI-for-age z-score



MEAN ABSOLUTE WITHIN-GROUP CHANGE IN BMI-FOR-AGE *z*-SCORE

TRIAL 6

- BMI-for-age z-score from baseline at Week 24 (n=57): +0.29 (95% CI 0.14, 0.45)[2]

EXTENSION STUDY

- BMI-for-age z-score from Trial 6 baseline to Week 96: +0.27 (95% CI 0.05, 0.48)[3]

Please click here to see the study limitations for Trial 6 and the Extension Study.

IMPORTANT SAFETY INFORMATION

Effect on Blood Pressure

- Increased blood pressure has been observed in some patients treated with ORKAMBI® (lumacaftor/ivacaftor). Blood pressure should be monitored periodically in all patients being treated with ORKAMBI

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12+

ORKAMBI® (lumacaftor/ivacaftor) studied in patients with CF age 12 years and older[1,8,9]

[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.[8]

- All patients remained on currently prescribed CF therapies[1,8]

PRIMARY ENDPOINT[1,8]

- Absolute change in ppFEV$_1$ from baseline at Week 24 assessed as the average of the treatment effects at Week 16 and at Week 24

SELECTED SECONDARY ENDPOINTS[1,8,9]

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

POOLED ANALYSIS[8]

- 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

KEY INCLUSION CRITERIA[8]

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

KEY EXCLUSION CRITERIA[1]

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

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

qd, each day.

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Trials 1 and 2 in patients age 12 years and older

Safety demonstrated in >1100 patients with CF in 2 Phase 3 trials[1]

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

Discontinuations due to adverse events[1]

- ORKAMBI 5%; placebo 2%

Serious adverse events[1]

- Serious adverse events, 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

LIVER-RELATED ADVERSE EVENTS[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 and those who received placebo
- Three patients who received ORKAMBI had liver-related serious adverse events, including 2 reported as transaminase elevations and 1 as hepatic encephalopathy, compared to none in the placebo group
  - Of these 3 patients, 1 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 pre-existing cirrhosis and/or portal hypertension who received ORKAMBI, worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy was observed in 1 patient
  - The event occurred within 5 days of the start of dosing and resolved following discontinuation of ORKAMBI

[a]Trials 1 and 2 were Phase 3, randomized, double-blind, placebo-controlled, 24-week studies in patients age 12 years and older with CF who were homozygous for the *F508del* mutation in the *CFTR* gene, were clinically stable, and had a ppFEV$_1$ between 40 and 90 at screening.[1]

IMPORTANT SAFETY INFORMATION

Drug Interactions

Substrates of CYP3A

- 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

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Safety demonstrated in >1100 patients with CF in 2 Phase 3 trials[1] (cont'd)

RESPIRATORY ADVERSE EVENTS

- In Trials 1 and 2, the incidence of respiratory symptom-related adverse events (eg, chest discomfort, dyspnea, and respiration abnormal) was more common in patients treated with ORKAMBI® (lumacaftor/ivacaftor) (22%) than in 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 events was more common in patients treated with ORKAMBI with lower pretreatment FEV_1
- Most respiratory symptom-related adverse events occurred within the first week of treatment and resolved within 2 to 3 weeks[5]
- During a 24-week, open-label, Phase 3b clinical trial in 46 patients age 12 years and older (Trial 5) with advanced lung disease ($ppFEV_1$ <40; mean $ppFEV_1$: 29.1 at baseline [range: 18.3-42.0]), the incidence of respiratory symptom-related adverse events was 65%[1]

MENSTRUAL ABNORMALITIES[1]

- In Trials 1 and 2, menstrual abnormalities (eg, amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular) were more common in female patients treated with ORKAMBI (10%) than in patients receiving placebo (2%)
- These events occurred more frequently in the subset of female patients treated with ORKAMBI who were using hormonal contraceptives (27%) compared with those not using hormonal contraceptives (3%)

INCREASED BLOOD PRESSURE[1]

- In Trials 1 and 2, adverse events related to increases in blood pressure (eg, 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 2 occasions was 3.6% and 2.2%, respectively, in patients treated with ORKAMBI compared with 1.6% and 0.5% in patients who received placebo

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

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Safety demonstrated in >1100 patients with CF in 2 Phase 3 trials[1] (cont'd)

COMMON ADVERSE EVENTS

ADVERSE EVENTS IN ≥5% OF PATIENTS TREATED WITH ORKAMBI® (LUMACAFTOR/IVACAFTOR) AND AT A HIGHER RATE THAN PLACEBO[1]

ADVERSE EVENT (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)

The safety profile from 2 pediatric trials in patients with CF age 6 through 11 years who were homozygous for the *F508del-CFTR* mutation—a 24-week, open-label, multicenter, Phase 3 safety trial in 58 patients (Trial 3) and a 24-week, placebo-controlled, Phase 3 clinical trial (Trial 4) in 204 patients (103 received lumacaftor 200 mg/ivacaftor 250 mg every 12 hours and 101 received placebo)—was similar to that observed in Trials 1 and 2. Adverse reactions that are not listed in the table above and that occurred in ≥5% of ORKAMBI-treated patients with an incidence of ≥3% higher than placebo included: productive cough (17.5% vs 5.9%), nasal congestion (16.5% vs 7.9%), headache (12.6% vs 8.9%), abdominal pain upper (12.6% vs 6.9%), and sputum increased (10.7% vs 2.0%).

In a 24-week, open-label, multicenter Phase 3 study in 60 patients age 2 through 5 years with CF who were homozygous for the *F508del-CFTR* mutation (Trial 6), the safety profile was similar to that observed in studies in patients age 6 years and older.

[a]Reported as chest tightness.[8]

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100/125 mg • 150/188 mg oral granules

Recommended oral granules dose for ORKAMBI® (lumacaftor/ivacaftor)

Recommended dose[1] (weight based)

- **<14 kg:** One packet containing lumacaftor 100 mg/ivacaftor 125 mg every 12 hours[a]

100 mg/125 mg oral granules

- **≥14 kg:** One packet containing lumacaftor 150 mg/ivacaftor 188 mg every 12 hours[a]

150 mg/188 mg oral granules

[a]14 kg≈31 lb.

ORKAMBI oral granules should be taken with fat-containing food[1]

- A safe and efficacious dose of ORKAMBI for patients age 2 years or younger has not been established. The use of ORKAMBI (oral granules) in children less than age 2 years is not recommended[1]

Patients should continue taking all of their prescribed CF therapies with ORKAMBI[1]

Please click for Important Safety Information and full Prescribing Information for ORKAMBI.

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Dosage adjustments for ORKAMBI® (lumacaftor/ivacaftor)

	Oral granules dose[1]	
Hepatic impairment		
Severe impairment (Child-Pugh Class C)[a]	1 packet in the morning or less frequently, no dose in the evening	
Moderate impairment (Child-Pugh Class B)	1 packet in the morning every day and 1 packet in the evening every other day	
Mild impairment (Child-Pugh Class A)	No dose adjustment required	
CYP3A inhibitors		
Initiating ORKAMBI in patients already taking a **strong** CYP3A inhibitor (eg, itraconazole)[b]	**First week**	**After first week**
	1 packet every other day	Continue with the full recommended daily dose as prescribed
Initiating CYP3A inhibitors in patients already taking ORKAMBI[c]	No dose adjustment required	
Dose interruptions of ORKAMBI while taking **strong** CYP3A inhibitors	If ORKAMBI is interrupted for more than 1 week and then reinitiated while taking strong CYP3A inhibitors, reduce dose to 1 packet every other day for the first week of treatment reinitiation. Following this period, continue with the full recommended daily dose as prescribed.	

[a]Use with caution after weighing the risks and benefits of treatment.[1]

[b]Additional examples include **ketoconazole, posaconazole, voriconazole, telithromycin,** and **clarithromycin**.[1]

[c]No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.[1]

Missed dose of oral granules[1]

- If **≤6 hours** have passed: Advise patient to take the dose with fat-containing food
- If **>6 hours** have passed: Advise patient to **skip that dose** and resume the normal schedule for the following dose. A double dose should **not** be taken to make up for the forgotten dose

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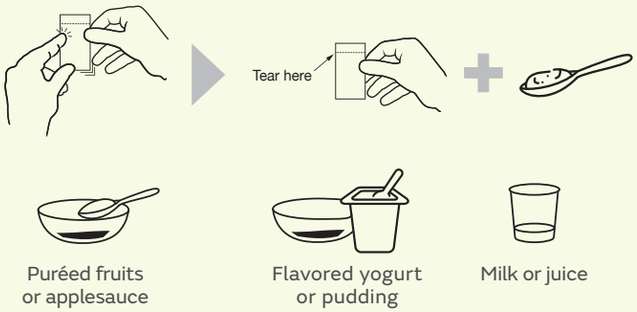
How to administer ORKAMBI® (lumacaftor/ivacaftor) oral granules

1 PREPARATION[1]

- Caregiver should hold the packet with the perforation on top, shake the packet gently to settle the granules, and tear or cut the packet open along the perforation
- Caregiver should mix all granules into 1 teaspoon (5 mL) of soft food or liquid
- Food or liquid should be at or below room temperature

Examples of soft foods or liquids include:



2 ADMINISTRATION[1]

- After mixing, caregiver should give within 1 hour
- Caregiver should make sure the child finishes the dose completely

3 GIVE WITH FAT-CONTAINING FOOD[1]

- Food that contains fat must be taken just before or after the oral granules dose

Examples of fat-containing foods include:

- Eggs
- Avocado
- Nuts
- Butter
- Peanut butter
- Cheese pizza
- Whole-milk dairy products (eg, whole milk, cheese, and yogurt)

It is important that patients consume the entire oral granules mixture with each dose[1]

PALATABILITY OF ORKAMBI ORAL GRANULES[10]

- Children may find the taste of the oral granules to be bitter
- Mixing the oral granules with soft foods or liquids that are sweet or rich, such as pudding or chocolate sauce, may help with the taste

Refer your patients to ORKAMBI.com for more information on administering ORKAMBI oral granules.

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References: 1. ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; July 2019. **2.** McNamara JJ, McColley SA, Marigowda G, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med.* 2019;7(4):325-335. **3.** Hoppe JE, Chilvers M, Ratjen F, et al. Long-term safety of lumacaftor–ivacaftor in children aged 2-5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study. *Lancet Respir Med.* Published online May 6, 2021. http://dx.doi.org/10.1016/S2213-2600(21)00069-2 **4.** Roach DJ, Crémillieux Y, Fleck RJ, et al. Ultrashort echo-time magnetic response imaging is a sensitive method for the evaluation of early cystic fibrosis lung disease. *Ann Am Thorac Soc.* 2016;13(11):1923-1931. **5.** Turovic L, Caudri D, Rosenow T, et al. Structural determinants of long-term functional outcomes in young children with cystic fibrosis. *Eur Respir J.* 2020;55(5):1900748. **6.** McNamara JJ, McColley SA, Marigowda G, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med* (suppl). 2019;7(4):325-335. **7.** Hoppe JE, Chilvers M, Ratjen F, et al. Long-term safety of lumacaftor-ivacaftor in children aged 2-5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study. *Lancet Respir Med* (suppl). Published online May 6, 2021. http://dx.doi.org/10.1016/S2213-2600(21)00069-2 **8.** Wainwright CE, Elborn JS, Ramsey BW, et al; for the 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. **9.** Wainwright CE, Elborn JS, Ramsey BW, et al; for the TRAFFIC and TRANSPORT Study Groups. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* (suppl). 2015;373(3):220-231. **10.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-3909; 2018.

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