ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

For patients with CF aged 1 year and older who are homozygous for the *F508del* mutation[1-4]

Modify the course.
Treat with ORKAMBI today.

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

INDICATION AND USAGE

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year 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.

Undetected structural lung disease in young patients often precedes signs and symptoms of CF[5]

EVIDENCE SUGGESTS THAT STRUCTURAL LUNG DAMAGE BEGINS AT A YOUNG AGE, IS PROGRESSIVE, AND REDUCES QUALITY OF LIFE[6]

- A study found that the prevalence of structural lung disease, most notably bronchiectasis and mucus plugging, increased early in life
- Bronchiectasis was observed in 33.1% of patients aged 1 to 2 years, and increased to 73.7% by age 5 to 6 years
- Mucus plugging was observed in 7.91% of patients aged 1 to 2 years, and increased to 37.13% by age 5 to 6 years

ANOTHER STUDY OF YOUNG CHILDREN WITH CF FOUND AIRWAY ABNORMALITIES IN ALMOST ALL THE PATIENTS EXAMINED[5]

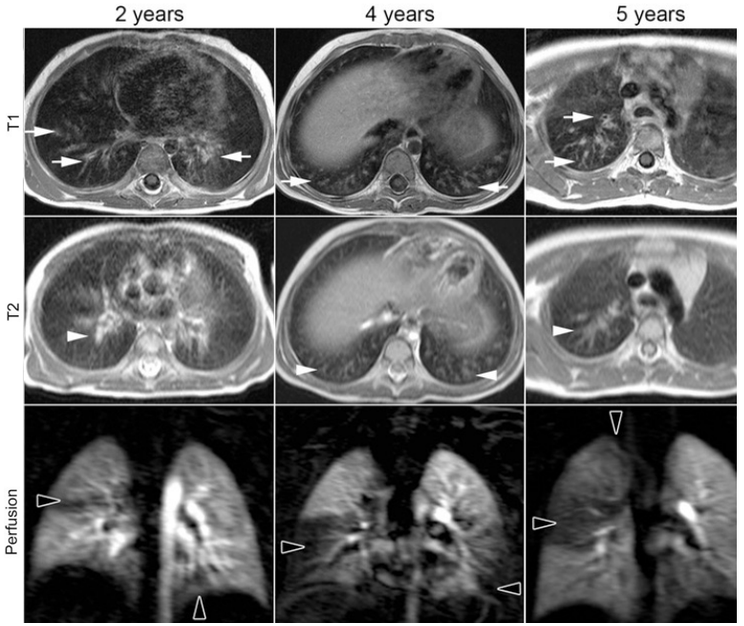


Figure 1 from: Wielpütz MO, et al. Magnetic resonance imaging detects changes in structure and perfusion, and response to therapy in early cystic fibrosis lung disease. *Am J Respir Crit Care Med*. 2014;189(8):956-965; reprinted with permission.

- Prospective, cross-sectional study aimed to evaluate the potential of MRI to detect abnormal lung structure and perfusion in young children with CF, and to monitor the response to therapy for pulmonary exacerbation
- MRI studies were performed in 50 children with CF, of which 40 were in stable clinical condition
- The MRI scans to the left show wall thickening and/or bronchiectasis (white arrows) and mucus plugging (white arrowheads)
- This study found that approximately 94% of the patients through age 5 had wall thickening/bronchiectasis changes found in MRI
- Approximately 83% of the patients through age 5 also had lung perfusion abnormalities

In a separate longitudinal study of patients with CF aged 2 months to 6.5 years, 44% had detectable bronchiectasis on their initial scan, which increased to 62% on a second subsequent scan about a year later[7]

MRI, magnetic resonance imaging.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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 >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 >3 x ULN when associated with bilirubin elevations >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

Hypersensitivity Reactions, Including Anaphylaxis

- Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported in the postmarketing setting. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue ORKAMBI and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with ORKAMBI

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 Important Safety Information and full Prescribing Information for ORKAMBI.

ORKAMBI®
(lumacaftor/ivacaftor)

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

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

- 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

Most Common Adverse Reactions

- 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 trial (Trial 3; N=58) and a placebo-controlled 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 trial (Trial 6; N=60) was similar to that in patients aged 6 years and older. The safety profile in patients age 1 through 2 years from an open-label trial (Trial 7; N=46) was similar to that in patients aged 2 years and older

USE IN SPECIFIC POPULATIONS

Pediatric Use

- The safety and effectiveness of ORKAMBI in patients with CF younger than 1 year of age have not been established

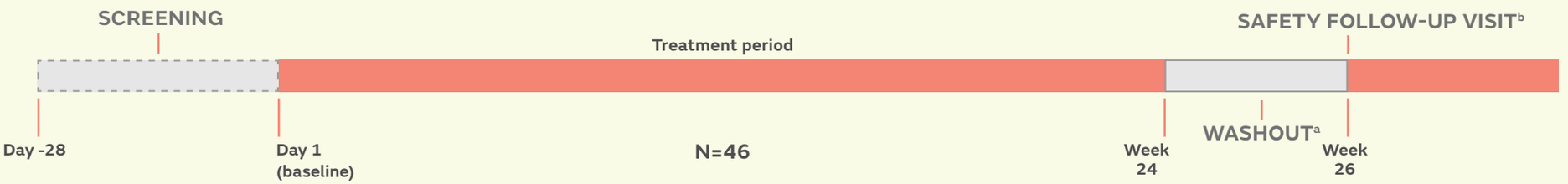
Please click for Important Safety Information and full Prescribing Information for ORKAMBI.

ORKAMBI®
(lumacaftor/ivacaftor)

A safety study was conducted in 46 patients with CF aged 1 through 2 years[1,2]

TRIAL 7 | OPEN-LABEL SAFETY STUDY (PART B)[1,2a]

EXTENSION STUDY



lumacaftor 75 mg/ivacaftor 94 mg q12h granules (7 to <9 kg; n=1)
lumacaftor 100 mg/ivacaftor 125 mg q12h granules (9 to <14 kg; n=44)
lumacaftor 150 mg/ivacaftor 188 mg q12h granules (≥14 kg; n=1)

SELECTED INCLUSION CRITERIA[2c]

- Confirmed CF diagnosis
- Homozygous for the *F508del* mutation
- Clinically stable
- Aged 1 to less than 2 years on Day 1 of the study
- Body weight within defined limits

PRIMARY ENDPOINT[2]

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

SECONDARY ENDPOINT[2]

- Absolute change from baseline in sweat chloride concentration at Week 24

[a]Patients remained on currently prescribed CF therapies (including during the washout), but did not receive ORKAMBI treatment during the washout period.[2]
[b]The safety follow-up visit was scheduled to occur 2 weeks (±4 days) after the last dose of ORKAMBI. For patients who enrolled in the optional open-label Extension Study, this visit was the Day 1 visit of the Extension Study.[2]
[c]Exclusion criteria included a history of cirrhosis with portal hypertension, liver function tests more than twice the ULN, or a history of organ transplantation.[2]
[d]Additional assessments within the primary endpoint were also studied.[2]

q12h, every 12 hours; ULN, upper limit of normal.

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

ORKAMBI®
(lumacaftor/ivacaftor)

Selected baseline characteristics for Trial 7[2]

- In Trial 7, patients were dosed according to weight
  - lumacaftor 75 mg/ivacaftor 94 mg q12h (n=1)
  - lumacaftor 100 mg/ivacaftor 125 mg q12h (n=44)
  - lumacaftor 150 mg/ivacaftor 188 mg q12h (n=1)

	ORKAMBI® (lumacaftor/ivacaftor) N=46
Age at baseline/Day 1 (months)	
Mean (SD)	18.1 (3.5)
Sex, n (%)	
Female	24 (52.2)
Baseline sweat chloride (mmol/L)	
Mean (SD)	104.2 (7.7)
Baseline weight (kg)	
Mean (SD)	11.3 (1.3)

TRIAL 7 LIMITATIONS AND DISCLOSURES

- 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

IMPACT OF COVID-19[2]

- Trial 7 was conducted during the COVID-19 pandemic. Vertex implemented safety measures, including at-home safety visits, to provide patients the opportunity to continue the study and minimize risk of COVID-19 exposure through travel

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

SD, standard deviation.

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

ORKAMBI® (lumacaftor/ivacaftor)

The safety profile of ORKAMBI® (lumacaftor/ivacaftor) in patients aged 1 through 2 years was similar to patients aged 2 years and older[1,2]

LIVER-RELATED AEs

	ORKAMBI N=46 (%)
ELEVATED ALT OR AST	
>3 x ULN	5 (10.9)
>5 x ULN	2 (4.3)
>8 x ULN	1 (2.2)

- No patients had total bilirubin levels >2 x ULN
- No patients experienced treatment interruptions due to transaminase elevations

DISCONTINUATIONS AND SERIOUS AEs

- One patient (2.2%) discontinued treatment with ORKAMBI due to an AE (transaminase elevations)
- Five patients (10.9%) experienced serious AEs (three with infective pulmonary exacerbations of CF, one with post-procedural fever, and one with DIOS), all of which were considered by study investigators to be mild or moderate in severity

RESPIRATORY-RELATED AEs

- One patient (2.2%) experienced a respiratory-related AE (dyspnea)
  - It occurred on Day 1 of Trial 7, resulting in treatment interruption. ORKAMBI use resumed as normal on Day 2, and the event did not recur

Please click here to see the study limitations for Trial 7.

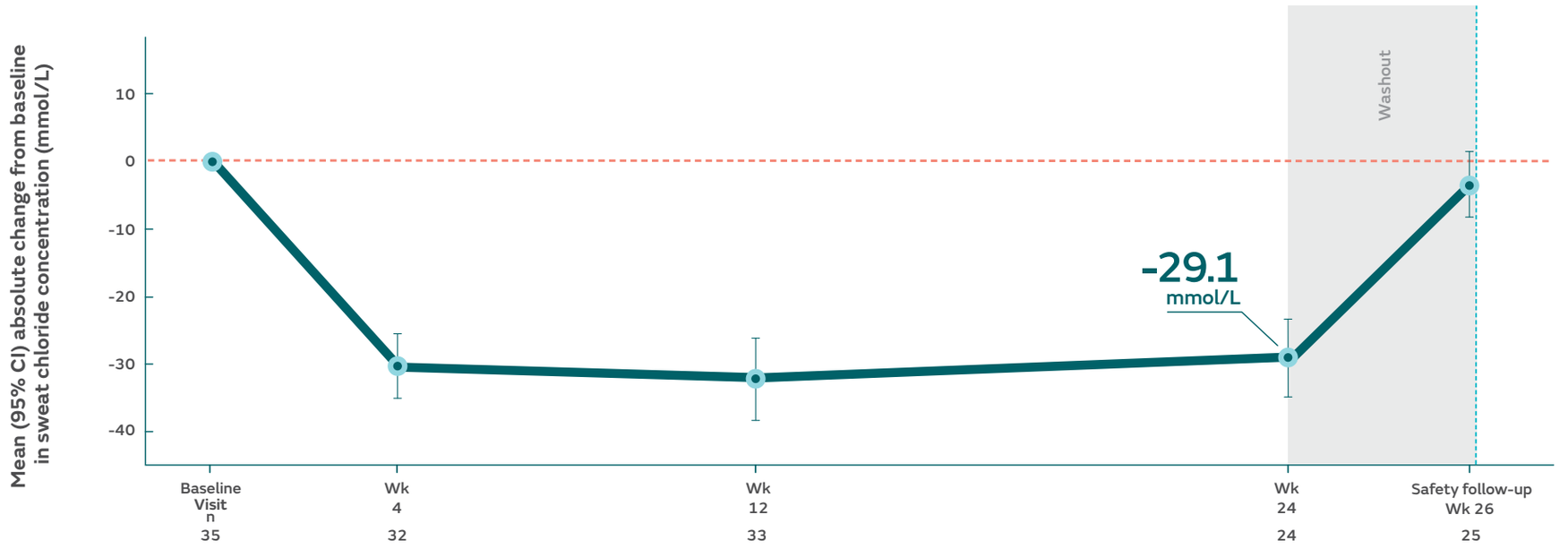
AE, adverse event; DIOS, distal intestinal obstruction syndrome.

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

ORKAMBI® (lumacaftor/ivacaftor)

In patients treated with ORKAMBI® (lumacaftor/ivacaftor), sweat chloride reductions were observed as early as Week 4[1,2]

Secondary endpoint: mean absolute change from baseline in sweat chloride concentration



MEAN ABSOLUTE CHANGE FROM BASELINE IN SWEAT CHLORIDE CONCENTRATION

- From baseline at Week 24 (n=24): -29.1 mmol/L (95% CI: -34.8, -23.4) reduction
- After washout, from Week 24 to Week 26 (n=25), increased to +27.3 mmol/L (95% CI: 22.3, 32.3)

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

Please click here to see study limitations for Trial 7.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

CI, confidence interval; Wk, week.

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

ORKAMBI®
(lumacaftor/ivacaftor)

A long-term safety study in patients with CF aged 2 through 5 years[1,3,4]

TRIAL 6 | OPEN-LABEL SAFETY STUDY[1,3]

EXTENSION STUDY | OPEN-LABEL EXTENSION STUDY OF TRIAL 6[4]

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

SELECTED INCLUSION CRITERIA[3,8b]

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

PRIMARY ENDPOINT[3]

- Safety and tolerability up to Week 24, including assessments of AEs and clinical laboratory values[c]

SELECTED SECONDARY ENDPOINTS[3]

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

SELECTED INCLUSION CRITERIA[4,9e]

- 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[4]

- Safety and tolerability up to Week 96, including assessments of AEs and clinical laboratory values[c]

SELECTED SECONDARY ENDPOINTS[4]

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

[a]Patients remained on currently prescribed CF therapies (including during the washout).[8]

[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.[8]

[c]Additional assessments within the primary endpoint were also studied.[3,4]

[d]Assessed at Week 24 and at Week 26 (after the washout).[1,3]

[e]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.[9]

BMI, body mass index.

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

ORKAMBI®
(lumacaftor/ivacaftor)

Selected baseline characteristics[3,4]

	TRIAL 6		EXTENSION STUDY
	ORKAMBI® (lumacaftor 100 mg/ ivacaftor 125 mg q12h) n=19 (Mean SD)	ORKAMBI (lumacaftor 150 mg/ ivacaftor 188 mg q12h) n=41 (Mean SD)	ORKAMBI N=57 (Mean SD)
Age, months	31.6 (5.1)	49.9 (10.6)	43.2 (12.2)
Sweat chloride, 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)

TRIAL 6 AND EXTENSION STUDY LIMITATIONS[3,4]

- 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

Long-term safety results in patients with CF aged 2 through 5 years[1,3,4,9]

Liver-related adverse events[1,9]

	TRIAL 6 N=60 (%)	EXTENSION STUDY N=57 (%)
ELEVATED ALT OR AST	ORKAMBI® (lumacaftor/ivacaftor)	
>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 both Trial 6 and the Extension Study, no patients had total bilirubin levels >2 x ULN[1,4]

DISCONTINUATIONS AND SERIOUS AEs

TRIAL 6[1,3]

- Three patients (5%) discontinued ORKAMBI treatment due to ALT/AST elevation
- Four patients (7%) experienced serious AEs (one with viral gastroenteritis, one with constipation, and two with infective pulmonary exacerbations of CF)

EXTENSION STUDY[4]

- Three patients (5%) discontinued due to AEs (one with viral gastritis and metabolic acidosis, one with pancreatitis and elevations in transaminases, and one with elevations in transaminases)
- Serious AEs 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%])

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

Overview of safety results from Trial 6 and the Extension Study[3,4,8]

Respiratory-related adverse events[4,8]

	TRIAL 6 N=60 (%)	EXTENSION STUDY N=57 (%)
ADVERSE EVENT	**ORKAMBI® (lumacaftor/ivacaftor)**	
Dyspnea	3 (5.0)	3 (5.0)
Wheezing	3 (5.0)	3 (5.0)
Chest discomfort	0	1 (2.0)
Respiration abnormal	1 (1.7)	1 (2.0)

TRIAL 6[3]

- No respiratory events led to treatment interruption or discontinuation

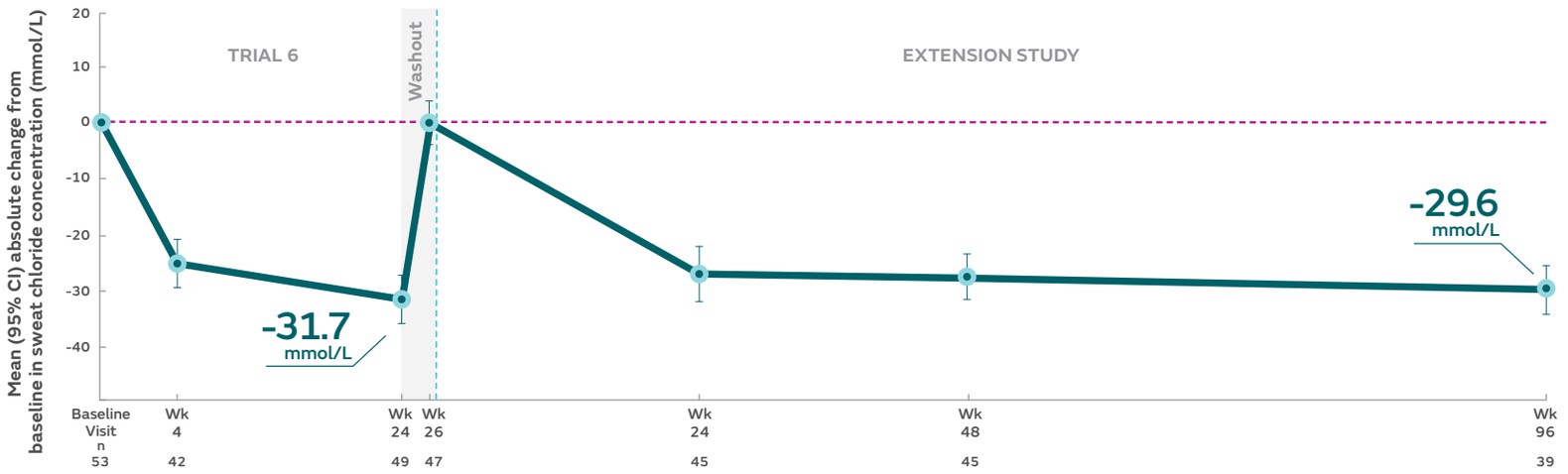
EXTENSION STUDY[4]

- No respiratory events led to treatment interruption or discontinuation

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

Sweat chloride results[1,3,4]

Secondary endpoint: absolute change from baseline in sweat chloride concentration



MEAN ABSOLUTE WITHIN-GROUP CHANGE IN SWEAT CHLORIDE CONCENTRATION

TRIAL 6[1,3]

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

EXTENSION STUDY[4]

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

There was no direct correlation between decrease in sweat chloride concentration 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

WARNINGS AND PRECAUTIONS (cont'd)

Liver-related Events

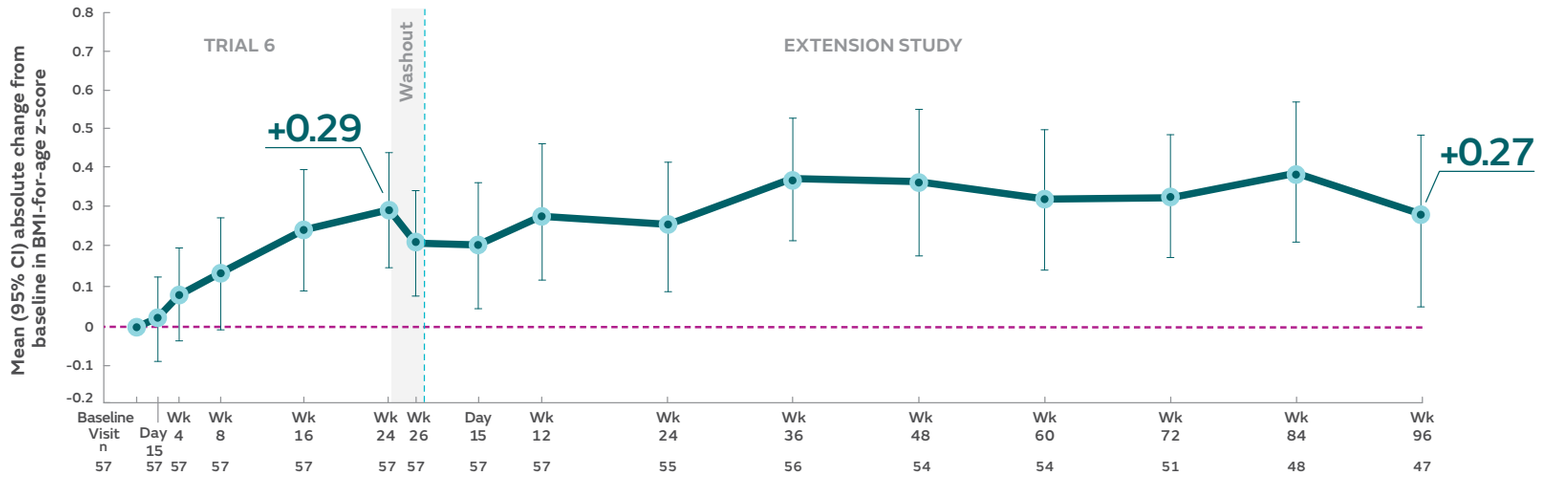
- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating 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 >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 >3 x ULN when associated with bilirubin elevations >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

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

ORKAMBI®
(lumacaftor/ivacaftor)

BMI-for-age z-score results[3,4]

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[3]

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

EXTENSION STUDY[4]

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions, Including Anaphylaxis

- Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported in the postmarketing setting. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue ORKAMBI and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with ORKAMBI

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 for Important Safety Information and full Prescribing Information for ORKAMBI.

ORKAMBI®
(lumacaftor/ivacaftor)

12+

ORKAMBI® (lumacaftor/ivacaftor) was studied in patients with CF aged 12 years and older[1,10,11]

TRIAL 1[a] Phase 3, randomized, double-blind	TRIAL 2[a] Phase 3, randomized, double-blind
24-WEEK TREATMENT	24-WEEK TREATMENT
ORKAMBI lumacaftor 400 mg/ivacaftor 250 mg q12h (n=182)	**ORKAMBI** lumacaftor 400 mg/ivacaftor 250 mg q12h (n=187)
PLACEBO (n=184)	**PLACEBO** (n=187)

[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.[10]

- All patients remained on currently prescribed CF therapies[1,10]

PRIMARY ENDPOINT[1,10]

- 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[1,10,11]

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[10]

- 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[10]

- ≥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*
- Three or more abnormal liver function tests (ALT, AST, AP, or GGT ≥3 x ULN, or total bilirubin ≥2 x ULN)

AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; qd, each day.

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

ORKAMBI® (lumacaftor/ivacaftor)

12+

Trials 1 and 2 in patients aged 12 years and older

Safety was demonstrated in >1100 patients with CF in two 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 AEs[1]

- ORKAMBI 5%; placebo 2%

Serious AEs[1]

- Serious AEs, 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 AEs[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 AEs, 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 aged 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]

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

ORKAMBI®
(lumacaftor/ivacaftor)

Trials 1 and 2 in patients aged 12 years and older

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

RESPIRATORY AEs

- In Trials 1 and 2, the incidence of respiratory symptom-related AEs (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%)
  - Respiration abnormal (chest tightness): ORKAMBI (9%) vs placebo (6%)
  - Dyspnea: ORKAMBI (13%) vs placebo (8%)
  - The incidence of these AEs was more common in patients treated with ORKAMBI with lower pretreatment FEV_1
- Most respiratory symptom-related AEs occurred within the first week of treatment and resolved within 2 to 3 weeks[10]
- During a 24-week, open-label 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: 18.3-42.0]), the incidence of respiratory symptom-related AEs was 65%

MENSTRUAL ABNORMALITIES

- 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

- In Trials 1 and 2, AEs 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

Trials 1 and 2 in patients aged 12 years and older

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

COMMON AEs[1]

ADVERSE EVENTS IN ≥5% OF PATIENTS TREATED WITH ORKAMBI® (lumacaftor/ivacaftor) AND AT A HIGHER RATE THAN PLACEBO

ADVERSE EVENT	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 aged 6 through 11 years who were homozygous for the *F508del-CFTR* mutation—a 24-week, open-label, multicenter safety trial in 58 patients (Trial 3) and a 24-week, placebo-controlled 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 patients treated with ORKAMBI 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 study in 60 patients aged 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 aged 6 years and older.

[a]Reported as chest tightness.[10]

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

ORKAMBI® (lumacaftor/ivacaftor)

Recommended dose for ORKAMBI® (lumacaftor/ivacaftor) oral granules[1]

RECOMMENDED DOSE FOR PATIENTS AGED 1 TO 2 YEARS (WEIGHT BASED)

7 to <9 kg: One packet containing lumacaftor 75 mg/ivacaftor 94 mg q12h[a]

9 to <14 kg: One packet containing lumacaftor 100 mg/ivacaftor 125 mg q12h[b]

≥14 kg: One packet containing lumacaftor 150 mg/ivacaftor 188 mg q12h

RECOMMENDED DOSE FOR PATIENTS AGED 2 TO 5 YEARS (WEIGHT BASED)

<14 kg: One packet containing lumacaftor 100 mg/ivacaftor 125 mg q12h

≥14 kg: One packet containing lumacaftor 150 mg/ivacaftor 188 mg q12h

[a]7-9 kg=15-20 lb.
[b]14 kg≈31 lb.

- A safe and efficacious dose of ORKAMBI for patients younger than 1 year has not been established. The use of ORKAMBI (oral granules) in children younger than 1 year is not recommended

- **ORKAMBI granules should be taken with fat-containing food**
- **Advise patients to avoid grapefruit products during the first week after treatment initiation with ORKAMBI**
- **Patients should continue taking all of their prescribed CF therapies with ORKAMBI**

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

ORKAMBI®
(lumacaftor/ivacaftor)

Oral granule dosage adjustments for ORKAMBI® (lumacaftor/ivacaftor)[1]

	Oral granules dose	
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[b]		
Initiating ORKAMBI in patients already taking a **strong** CYP3A inhibitor (eg, itraconazole)[c]	**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[d]	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.
[b]Advise patients to avoid grapefruit products during the first week after treatment initiation with ORKAMBI.
[c]Additional examples include **ketoconazole, posaconazole, voriconazole, telithromycin,** and **clarithromycin**.
[d]No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.

Missed dose of oral granules

- 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 missed dose

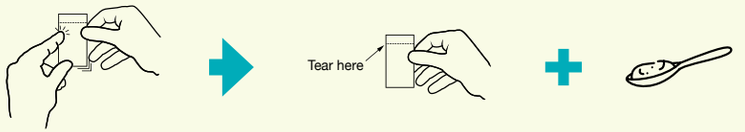
Please click for Important Safety Information and full Prescribing Information for ORKAMBI.

ORKAMBI®
(lumacaftor/ivacaftor)

How to administer ORKAMBI® (lumacaftor/ivacaftor) oral granules[1]

1 PREPARATION

- 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



Note: Examples of soft foods or liquids include:


Puréed fruits or applesauce


Flavored yogurt, syrups, or pudding


Milk or juice

2 ADMINISTRATION

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

3 GIVE WITH FAT-CONTAINING FOOD

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

Examples of fat-containing foods include:

- Breast milk or infant formula
- Yogurt[a]
- Cheese pizza[a]
- Cheese[a]
- Butter
- Eggs
- Whole milk
- Peanut butter

Keep your patients' age in mind when recommending fat-containing foods to caregivers.

[a]Be sure that cheeses and yogurts are made with whole milk.

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

PALATABILITY OF ORKAMBI ORAL GRANULES[12]

- Children may find the taste of the oral granules to be bitter
- Mixing the 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' caregivers to ORKAMBI.com for more information on administering ORKAMBI oral granules.

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

ORKAMBI®
(lumacaftor/ivacaftor)

Summary results for ORKAMBI® (lumacaftor/ivacaftor)

Patients aged 1 through 2 years homozygous for the *F508del* mutation — TRIAL 7[1,2]

PRIMARY ENDPOINT:

The safety profile of ORKAMBI in patients aged 1 through 2 years was similar to the established safety profile in patients aged 2 years and older. No new safety concerns were identified.

SECONDARY ENDPOINT:

Sweat chloride ↓ **-29.1** mmol/L

Absolute change from baseline in sweat chloride at Week 24 (95% CI: -34.8, -23.4). Sweat chloride reductions seen were similar to reductions seen in patients aged 2 through 5 years.

Patients aged 2 through 5 years homozygous for the *F508del* mutation — TRIAL 6/EXTENSION STUDY[3,4]

PRIMARY ENDPOINT:

The safety data for ORKAMBI in patients aged 2 through 5 years were similar with the well-characterized safety profile observed in patients in older age groups. The safety data remained consistent through 96 weeks in the Extension Study of Trial 6.

SECONDARY ENDPOINT:

Sweat chloride ↓ **-31.7** mmol/L

Absolute change from baseline in sweat chloride at Week 24 (95% CI: -35.7, -27.6). Reductions in sweat chloride were generally maintained through Week 96 in the Extension Study.

- There was no direct correlation between decrease in sweat chloride levels and improvement in lung function ($ppFEV_1$)[1]
- The study was open label and not placebo controlled; therefore, causality cannot be attributed

SAFETY RESULTS for patients 12 years and older[1]

- The overall safety profile of ORKAMBI in patients 12 years and older is based on pooled data from Trials 1 and 2
- The most common AEs in ≥5% of patients 12 years and older treated with ORKAMBI and at a higher rate than placebo include dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal (chest tightness), blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza

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

ORKAMBI® (lumacaftor/ivacaftor)

References: 1. ORKAMBI [prescribing information]. Boston, MA. Vertex Pharmaceuticals Incorporated; August 2023. **2.** Rayment JH, Asfour F, Rosenfeld M, et al; VX16-809-122 Study Group. A phase 3, open-label study of lumacaftor/ivacaftor in children 1 to less than 2 years of age with cystic fibrosis homozygous for *F508del-CFTR. Am J Respir Crit Care Med*. Published online June 30, 2022. doi:10.1164/rccm.202204-0734OC **3.** 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. doi:10.1016/S2213-2600(18)30460-0 **4.** 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 **5.** Wielpütz MO, Puderbach M, Kopp-Schneider A, et al. Magnetic resonance imaging detects changes in structure and perfusion, and response to therapy in early cystic fibrosis lung disease. *Am J Respir Crit Care Med.* 2014;189(8):956-965. doi:10.1164/rccm.201309-1659OC **6.** Turkovic 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. doi:10.1016/S2213-2600(18)30460-0 **7.** Mott LS, Park J, Murray CP, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. *Thorax*. 2012;67(6):509-516. doi:10.1136/thoraxjnl-2011-200912 **8.** 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. **9.** 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 **10.** 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. **11.** 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. **12.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-3909; 2018.

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100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules