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

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

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.

Click here for Important Safety Information and full Prescribing Information.
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 FEV1 (ppFEV1) <40). Clinical experience in patients with ppFEV1 <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.

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 2 through 5 years from an open-label Phase 3 trial (Trial 4; 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.
ORKAMBI® (lumacaftor/ivacaftor) was studied in patients age 2 through 5 years.

### Key Exclusion Criteria
- Hemoglobin <10 g/dL
- ALT, AST, or total bilirubin >2 x ULN
- Abnormal renal function
- An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1
- History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant

### Key Inclusion Criteria
- Confirmed CF diagnosis, F508del homozygous, clinically stable, 2 through 5 years of age
- Body weight ≥8 kg at screening

### Primary Endpoint
- Safety and tolerability up to Week 24, including assessments of adverse events, clinical laboratory values, and spirometry

### Secondary Endpoints
- Absolute change from baseline at 24 weeks for: sweat chloride level, BMI, and BMI z-score

### 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.

### Trial 6 Limitations
- 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

### Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>ORKAMBI (lumacaftor 100 mg/ivacaftor 125 mg q12h) n=19</th>
<th>ORKAMBI (lumacaftor 150 mg/ivacaftor 188 mg q12h) n=41</th>
<th>ORKAMBI TOTAL N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, months (range)</td>
<td>31.6 (24-40)</td>
<td>49.9 (25-69)</td>
</tr>
<tr>
<td>SwCl, mmol/L (range)</td>
<td>105.5 (84.0-120.0)</td>
<td>106.0 (89.0-121.3)</td>
</tr>
<tr>
<td>BMI, kg/m² (range)</td>
<td>15.99 (13.84-17.62)</td>
<td>15.98 (13.14-17.92)</td>
</tr>
<tr>
<td>BMI z-score (range)</td>
<td>-0.10 (-2.17-1.10)</td>
<td>0.30 (-2.16-1.50)</td>
</tr>
</tbody>
</table>

### Trial 6 Design

#### Screening
- Lumacaftor 100 mg/ivacaftor 125 mg q12h granules (<14 kg; n=19) or lumacaftor 150 mg/ivacaftor 188 mg q12h granules (≥14 kg; n=41)

#### Washout
- Day -28

#### Baseline
- N=60

#### Week 24

#### Week 26

- Patients remained on currently prescribed CF therapies (including during the washout)

#### Key Inclusion Criteria
- Confirmed CF diagnosis, F508del homozygous, clinically stable, 2 through 5 years of age
- Body weight ≥8 kg at screening

#### Primary Endpoint
- Safety and tolerability up to Week 24, including assessments of adverse events, clinical laboratory values, and spirometry

#### Selected Secondary Endpoints
- Absolute change from baseline at 24 weeks for: sweat chloride level, BMI, and BMI z-score

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*Key exclusion criteria included hemoglobin <10 g/dL, ALT, AST, or total bilirubin >2 x ULN, abnormal renal function, an 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.

*Assessed at Week 24 and at Week 26.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; q12h, every 12 hours; SwCl, sweat chloride; ULN, upper limit of normal.

Click here for Important Safety Information and full Prescribing Information.
Overview of safety results from Trial 6

**DISCONTINUATIONS AND SERIOUS ADVERSE EVENTS**

- 3 patients (5%) discontinued due to adverse events (3 with transaminase elevations)
- 4 patients (6.7%) experienced serious adverse events (1 with gastroenteritis viral, 1 with constipation, and 2 with infective pulmonary exacerbations of CF)

**IMPORTANT SAFETY INFORMATION**

**Liver-related Events**

- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI® (lumacaftor/ivacaftor). 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.
- Median time to onset of first event was 2 days and median duration of the events was 1.5 days
- No respiratory events led to treatment interruption or discontinuation

**Liver-related adverse reactions**

<table>
<thead>
<tr>
<th>ELEVATED ALT OR AST</th>
<th>ORKAMBI TOTAL, N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ALT &gt;3 x ULN) or (AST &gt;3 x ULN)</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td>(ALT &gt;5 x ULN) or (AST &gt;5 x ULN)</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>(ALT &gt;8 x ULN) or (AST &gt;8 x ULN)</td>
<td>5 (8.3)</td>
</tr>
</tbody>
</table>

**Respiratory symptom-related adverse reactions**

- 3 patients discontinued lumacaftor/ivacaftor treatment permanently due to transaminase elevations

Click here for Important Safety Information and full Prescribing Information.
Sweat chloride results (pharmacodynamics)

MEAN ABSOLUTE WITHIN-GROUP CHANGE IN SWEAT CHLORIDE

- From baseline at Week 24 (n=49): -31.7 mmol/L (95% CI -35.7, -27.6) reduction\(^1,5\)
- After washout, from Week 24 to Week 26 (n=48): +33.0 mmol/L (95% CI 28.9, 37.1)\(^1,5\)
- There was no direct correlation between decrease in sweat chloride levels and improvement in lung function (ppFEV\(_1\))\(^1\)

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\(^\circledR\) (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.

Click here for Important Safety Information and full Prescribing Information.

BMI z-score and BMI results

MEAN ABSOLUTE WITHIN-GROUP CHANGE IN BMI z-SCORE

- For BMI z-score from baseline at Week 24 (n=57): +0.29 (95% CI 0.14, 0.45)\(^1\)
- For BMI from baseline at Week 24 (n=57): +0.27 (95% CI 0.07, 0.47)\(^1\)

IMPORTANT SAFETY INFORMATION

Effect on Blood Pressure

- Increased blood pressure has been observed in some patients treated with ORKAMBI\(^\circledR\) (lumacaftor/ivacaftor). Blood pressure should be monitored periodically in all patients being treated with ORKAMBI.
SAFETY (PRIMARY ENDPOINT)

60 PATIENTS AGE 2 THROUGH 5 YEARS WERE STUDIED IN TRIAL 6

• The safety profile was similar to that in patients aged 6 years and older
• Serious adverse reactions included gastroenteritis viral, constipation, and infective pulmonary exacerbation of CF

DESCRIPTION OF SELECTED ADVERSE DRUG REACTIONS

• 3 patients (5%) had respiratory symptom-related adverse events
  – No respiratory events led to treatment interruption/discontinuation
• 9 patients (15%) had elevated transaminases (>3 x ULN)
• 3 patients (5%) discontinued from the study, all due to transaminase elevations

SUMMARY OF SELECTED SECONDARY ENDPOINT RESULTS

MEAN ABSOLUTE CHANGE FROM BASELINE AT 24 WEEKS (WITHIN-GROUP)

- Sweat chloride
  -31.7 mmol/L (95% CI -35.7, -27.6)

+ BMI z-score
  +0.29 (95% CI 0.14, 0.45)

LIMITATIONS

• 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

ORKAMBI® (lumacaftor/ivacaftor) oral granules are small white to off-white granules
ORKAMBI® (lumacaftor/ivacaftor) was studied in over 250 patients age 6 through 11 years.

### TRIAL 3 | PHASE 3, OPEN-LABEL SAFETY STUDY

24 WEEKS (FOLLOWED BY 2-WEEK WASHOUT)

- **KEY INCLUSION CRITERIA**
  - Confirmed CF diagnosis, F508del homozygous, clinically stable, 6 through 11 years of age
  - Percent predicted FEV1 >40%

- **PRIMARY ENDPOINT**
  - Safety and tolerability, including assessments of adverse events, clinical laboratory values, and spirometry (FEV1) up to 24 weeks

- **ADDITIONAL ASSESSMENTS**
  - Absolute change in sweat chloride:
    - From baseline at Day 15 and at Week 24
    - From Week 24 at Week 26 (washout period)

- **Trial Participants**
  - ORKAMBI lumacaftor 200 mg/ivacaftor 250 mg q12h (n=58)
  - WASHOUT
  - Placebo q12h (n=101)

### TRIAL 4 | PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED EFFICACY AND SAFETY STUDY

24 WEEKS

- **KEY INCLUSION CRITERIA**
  - Confirmed CF diagnosis, F508del homozygous, clinically stable, 6 through 11 years of age
  - Screening LCI score ≥7.5
  - Percent predicted FEV1 ≥70%

- **PRIMARY ENDPOINT**
  - Absolute change in LCI2.5 from baseline through Week 24

- **ADDITIONAL ASSESSMENTS**
  - Key Secondary Endpoints
    - Absolute change from baseline:
      - LCI2.5
      - Sweat chloride
      - BMI
      - CFQ-R Respiratory Domain score
  - Other Secondary Endpoints
    - Absolute change from baseline:
      - ppFEV1
      - BMI
      - Sweat chloride

- **Trial Participants**
  - ORKAMBI lumacaftor 200 mg/ivacaftor 250 mg q12h (n=103)
  - Placebo q12h (n=101)

### EXTENSION STUDY | OPEN-LABEL EXTENSION OF TRIALS 3 AND 4

96 WEEKS

- **KEY INCLUSION CRITERIA**
  - Completed Trial 3 (including washout) or Trial 4
  - Safety and tolerability of long-term treatment, including assessments of adverse events, clinical laboratory values, and spirometry

- **Trial Participants**
  - Continued ORKAMBI (ORKAMBI ® ORKAMBI) lumacaftor 200 mg/ivacaftor 250 mg q12h (n=201)
  - Started ORKAMBI (Placebo ® ORKAMBI) lumacaftor 200 mg/ivacaftor 250 mg q12h (n=203)

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*Power for secondary endpoints, including key secondary endpoints, was limited. Analysis of secondary endpoints was not adjusted for multiplicity. CFQ-R, Cystic Fibrosis Questionnaire-Revised.*
Limitations and disclosures

LIMITATIONS OF TRIAL 3
• The study was open label and not placebo controlled; therefore, causality cannot be attributed to drug effect.

LIMITATIONS OF THE EXTENSION STUDY
• The study was open label and not placebo controlled; therefore, causality cannot be attributed to drug effect.
• All patients in the study knew they were on active drug, which may have introduced bias related to awareness of treatment.
• Enrollment in the Extension Study was limited only to those patients who met strict inclusion criteria, completed Trials 3 or 4, and elected to enroll in the Extension Study.
• Rare adverse events may not have been detected.

ADDITIONAL DISCLOSURES
• The Trial 4 efficacy results and the Extension Study are not included in the approved full Prescribing Information, and the FDA did not consider either study in approving ORKAMBI® (lumacaftor/ivacaftor).
• The Extension Study may not meet the FDA definition of an adequate and well-controlled study due to its study design.

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.

Baseline characteristics of Trials 3 and 4

- The following trials for ORKAMBI® (lumacaftor/ivacaftor) were conducted in different patient populations and are not meant to be comparative.

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTICS</th>
<th>TRIAL 3 24 WEEKS</th>
<th>TRIAL 4 24 WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female, %</td>
<td>53.4</td>
<td>61.2</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>9.1 (6-12)</td>
<td>8.7 (6-12)</td>
</tr>
<tr>
<td>Mean percent predicted FEV1 (range)</td>
<td>91.4 (55.0-122.7)</td>
<td>88.8 (48.6-119.6)</td>
</tr>
<tr>
<td>Mean sweat chloride, mmol/L (range)</td>
<td>105.9 (57.0-121.3)</td>
<td>102.6 (46.0-119.0)</td>
</tr>
<tr>
<td>Mean LCI2.5 score (range)</td>
<td>—</td>
<td>10.3 (7.10-18.38)</td>
</tr>
<tr>
<td>Mean BMI z-score (range)</td>
<td>—</td>
<td>-0.14 (-3.24 to 1.54)</td>
</tr>
</tbody>
</table>

- At baseline in Trial 4, 97.1% of patients treated with ORKAMBI had abnormal LCI2.5 (≥7.5); mean percent predicted FEV1 was 88.8.

PATIENTS FROM TRIALS 3 AND 4 WERE ELIGIBLE TO ENROLL IN THE EXTENSION STUDY
- Of 262 eligible patients from Trials 3 and 4, 240 (91.6%) enrolled in the Extension Study.
- Of 240 patients enrolled in the Extension Study, 96 previously received placebo and 143 previously received ORKAMBI.
- Data are reported for 239 patients who received at least 1 dose of ORKAMBI.

Click here for Important Safety Information and full Prescribing Information.
Safety profile: Trials 3, 4, and the Extension Study

DISCONTINUATIONS DUE TO ADVERSE EVENTS

- **Trial 3**: 3.4% (n=2); due to elevated liver transaminases (1) and rash (1)
- **Trial 4**: 3% (n=3) in the ORKAMBI® (lumacaftor/ivacaftor) group due to respiration abnormal (1) and elevated transaminases (2); 2% (n=2) in the placebo group—both were due to elevated transaminases
- **Extension Study**: 3.8% (n=9); Placebo group had 1 case of urticaria and hot flush (1), elevated AST, ALT (4), autoimmune hepatitis (1), and CF hepatic disease (1); ORKAMBI group had gastrointestinal disorder (abdominal pain diarrhea/vomiting) (2), FEV1 decreased, respiration abnormal, asthma (1)

SERIOUS ADVERSE REACTIONS

- **Trial 3**: 6.9% (n=4); included infective pulmonary exacerbation (2), ileus (1), and elevated liver transaminase levels (1)
- **Trial 4**: 13% (n=13) in the ORKAMBI group had serious adverse events, of which 2 (1 drug interaction and 1 obstructive airway disorder) were considered treatment related. 11% (n=11) in the placebo group had serious adverse events, of which 3 (1 DIO and 2 elevated aminotransferases) were considered treatment related
- **Extension Study**: 30.2% (n=29) of patients in the placebo group and 30.1% (n=43) in the ORKAMBI group had at least 1 serious adverse event. 8 had serious adverse events considered related to study drug. Infective pulmonary exacerbations of cystic fibrosis occurred in 15.6% (n=15) of patients in the placebo group and 23.8% (n=34) of patients in the ORKAMBI group
  - 0.8% (n=2) of patients had at least 1 adverse event of elevated transaminases. The overall nature and incidence of liver events were consistent with Trials 3 and 4
  - 3.8% (n=9) of patients had cataracts/lens opacities, which were not considered visually significant and did not lead to study drug interruption or discontinuation. All lens findings were either present at Trial 3 or 4 baseline, resolved with continued treatment, or had confounding risk factors (e.g., corticosteroid use or family history)

Liver-related adverse reactions

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TRIAL 3 24 WEEKS (%)</th>
<th>TRIAL 4 24 WEEKS (%)</th>
<th>EXTENSION STUDY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST</td>
<td>ORKAMBI</td>
<td>ORKAMBI</td>
<td>Placebo</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
<td>3/57 (5.3)</td>
<td>1/103 (1.0)</td>
<td>2/101 (2.0)</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>5/57 (8.8)</td>
<td>5/103 (4.9)</td>
<td>3/101 (3.0)</td>
</tr>
<tr>
<td>&gt;3 x ULN</td>
<td>11/57 (19.3)</td>
<td>13/103 (12.6)</td>
<td>8/101 (7.9)</td>
</tr>
<tr>
<td>Discontinuation due to transaminase elevations</td>
<td>1/57 (1.8)</td>
<td>2/103 (1.9)</td>
<td>2/101 (2.0)</td>
</tr>
</tbody>
</table>

- In Trials 3 and 4 and the Extension Study, no patients had an increase in total bilirubin levels >2 x ULN
- In the Extension Study, 3 patients had other liver-related events, including 2 adverse events of hepatitis and 1 serious adverse event of autoimmune hepatitis

Respiratory adverse reactions

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TRIAL 3 24 WEEKS (%)</th>
<th>TRIAL 4 24 WEEKS (%)</th>
<th>EXTENSION STUDY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>1/58 (1.7)</td>
<td>5/103 (5.0)</td>
<td>5/101 (5.0)</td>
</tr>
<tr>
<td>Respiration abnormal</td>
<td>1/58 (1.7)</td>
<td>6/103 (6.0)</td>
<td>4/101 (4.0)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>0/58 (0)</td>
<td>1/103 (1.0)</td>
<td>0/101 (0)</td>
</tr>
</tbody>
</table>

- These trials were conducted in different patient populations and are not meant to be comparative

Potentially Clinically Significant (PCS) Laboratory Tests

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TRIAL 3 24 WEEKS (%)</th>
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<th>EXTENSION STUDY (%)</th>
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Click here for Important Safety Information and full Prescribing Information.
### COMMON ADVERSE REACTIONS IN TRIAL 3

**Most frequently observed treatment-emergent adverse events in ≥10% of patients**[^1]

<table>
<thead>
<tr>
<th>Event</th>
<th>ORKAMBI (n=58)</th>
<th>Placebo (n=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs, n (%)</td>
<td>55 (94.9)</td>
<td>50 (51.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (50.0)</td>
<td>16 (16.7)</td>
</tr>
<tr>
<td>Infective pulmonary exacerbation</td>
<td>12 (20.7)</td>
<td>10 (10.4)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>12 (20.7)</td>
<td>10 (10.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (20.7)</td>
<td>10 (10.4)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8 (13.8)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>8 (13.8)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>7 (12.1)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (10.3)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (10.3)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (10.3)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (10.3)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (10.3)</td>
<td>5 (5.2)</td>
</tr>
</tbody>
</table>

[^1]: Trial 3 Safety Set. TEAE, treatment-emergent adverse event.

### COMMON ADVERSE REACTIONS IN TRIAL 4

**Most frequently observed treatment-emergent adverse events in ≥5% of patients in the ORKAMBI arm and ≥3% higher than placebo**[^15]

<table>
<thead>
<tr>
<th>Event</th>
<th>ORKAMBI (n=103)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs, n (%)</td>
<td>98 (95.1)</td>
<td>98 (97.0)</td>
</tr>
<tr>
<td>Productive cough</td>
<td>18 (17.5)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>17 (16.5)</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>15 (14.6)</td>
<td>10 (9.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (12.6)</td>
<td>9 (8.9)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>13 (12.6)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>11 (10.7)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>10 (9.7)</td>
<td>5 (5.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (5.8)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

[^15]: Trial 4 Safety Set.

---

Safety profile in Trials 3 and 4 was similar to that observed in patients age 12 years and older (see pages 32-34)[^1].

---

### COMMON ADVERSE REACTIONS IN THE EXTENSION STUDY

**Most frequently observed treatment-emergent adverse events in ≥10% of patients**[^15]

<table>
<thead>
<tr>
<th>Event</th>
<th>ORKAMBI—ORKAMBI (n=143)</th>
<th>Placebo—ORKAMBI (n=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs, n (%)</td>
<td>142 (99.3)</td>
<td>94 (97.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>91 (63.6)</td>
<td>64 (66.7)</td>
</tr>
<tr>
<td>Infective pulmonary exacerbation</td>
<td>75 (52.4)</td>
<td>43 (44.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>45 (31.5)</td>
<td>27 (28.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>36 (25.2)</td>
<td>13 (13.5)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>34 (23.8)</td>
<td>21 (21.9)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>32 (22.4)</td>
<td>18 (18.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (21.0)</td>
<td>15 (15.6)</td>
</tr>
<tr>
<td>Bacterial test positive</td>
<td>30 (21.0)</td>
<td>16 (16.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>29 (20.3)</td>
<td>26 (27.1)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>24 (16.8)</td>
<td>13 (13.5)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>22 (15.4)</td>
<td>21 (21.9)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>22 (15.4)</td>
<td>20 (20.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (14.7)</td>
<td>16 (16.7)</td>
</tr>
<tr>
<td>Vinal upper respiratory tract infection</td>
<td>21 (14.7)</td>
<td>15 (15.6)</td>
</tr>
<tr>
<td>Productive cough</td>
<td>19 (13.3)</td>
<td>15 (15.6)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>18 (12.6)</td>
<td>7 (7.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17 (11.9)</td>
<td>19 (19.8)</td>
</tr>
<tr>
<td>AST increased</td>
<td>17 (11.9)</td>
<td>15 (15.6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>17 (11.9)</td>
<td>8 (8.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (11.2)</td>
<td>8 (8.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (10.5)</td>
<td>11 (11.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (9.1)</td>
<td>11 (11.5)</td>
</tr>
</tbody>
</table>

Please see page 14 for Limitations and Disclosures of Trials 3, 4, and the Extension Study.

Click here for Important Safety Information and full Prescribing Information.
Improvements in lung function (LCI<sub>2.5</sub>) through 24 weeks

**TRIAL 4 | STATISTICALLY SIGNIFICANT IMPROVEMENT THROUGH WEEK 24 VS PLACEBO<sup>2</sup>**

<table>
<thead>
<tr>
<th>Visit</th>
<th>ORKAMBI (n=103)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ext Wk 4</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Ext Day 15</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Ext Wk 96</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Ext Wk 48</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Ext Wk 24</td>
<td>88</td>
<td>89</td>
</tr>
</tbody>
</table>

Mean Absolute Change in LCI<sub>2.5</sub> From Baseline Through Extension Week 96<sup>19</sup>

*Mean Absolute Change From Baseline in LCI<sub>2.5</sub> LS Mean (95% CI)

**EXTENSION STUDY | LCI<sub>2.5</sub> CHANGES<sup>19</sup>**

- The Extension Study included patients from Trial 3, where LCI was an exploratory endpoint in a subgroup (n=27)<sup>7</sup>
- ORKAMBI® → ORKAMBI: -0.85 point (95% CI -1.25, -0.45) LS mean change from baseline<sup>19</sup>
- Placebo → ORKAMBI: -0.86 point (95% CI -1.33, -0.38) LS mean change from baseline<sup>19</sup>

Please see page 14 for Limitations and Disclosures of Trials 3, 4, and the Extension Study

**IMPORTANT SAFETY INFORMATION**

Liver-related Events (cont)
- 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 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

Click here for Important Safety Information and full Prescribing Information.
Lung function (ppFEV₁) through 24 weeks

**TRIAL 3** | **ppFEV₁ AT WEEK 24 (PART OF THE SAFETY ASSESSMENT)**
- +2.5% point LS mean absolute change in ppFEV₁
- -3.2% point LS mean absolute change in ppFEV₁ from Week 24 at Week 26 (washout)

**TRIAL 4** | **IMPROVEMENT IN ppFEV₁ THROUGH WEEK 24 VS PLACEBO**
- +2.4% LS mean absolute improvement in ppFEV₁ from baseline through Week 24 compared to placebo
- Power for secondary endpoints was limited. Analysis of secondary endpoints was not adjusted for multiplicity

**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 FEV₁ (ppFEV₁) <40). Clinical experience in patients with ppFEV₁ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

**EXTENSION STUDY** | **ppFEV₁ CHANGES**

Mean Absolute Change in ppFEV₁ From Baseline Through Extension Week 96

- ORKAMBI: +3.1% point (95% CI 1.0, 5.1) LS mean change from baseline
- Placebo: +0.0% point (95% CI -2.7, 2.7) LS mean change from baseline

*Baseline was from Trial 3 or 4.

Please see page 14 for Limitations and Disclosures of Trials 3, 4, and the Extension Study

Click here for Important Safety Information and full Prescribing Information.
Sweat chloride results for the Extension Study (pharmacodynamics)

- **ORKAMBI**
  - Baseline: -24.8 mmol/L LS mean within-group improvement at Week 24
  - Washout: +21.3 mmol/L LS mean within-group absolute change from Week 24 at Week 26

- **Placebo**
  - Baseline: +21.3 mmol/L LS mean within-group absolute change from Week 24 at Week 26

**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.

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

Click here for Important Safety Information and full Prescribing Information.
BMI through 24 weeks

TRIAL 3 | RESULTS FOR BMI

- +0.64 kg/m² LS mean absolute change in BMI from baseline at Week 24

TRIAL 4 | BMI RESULTS THROUGH 24 WEEKS

Absolute Change From Baseline in BMI by Visit

Baseline Day 15 Wk 4 Wk 8 Wk 16 Wk 24
ORKAMBI (n=103)                Placebo (n=101)
-0.1 0.1 0.2 0.4 0.3 0.5 0.6

TRIAL 4 | BMI RESULTS THROUGH 24 WEEKS

Absolute Change From Baseline in BMI (kg/m²) LS Mean

Ext Wk 4 Ext Day 15 Ext Wk 96 Ext Wk 24 Ext Day 1 Ext Wk 8 Ext Wk 16 Ext Wk 48 Ext Wk 36 Ext Wk 60 Ext Wk 72 Ext Wk 84
ORKAMBI (n=161)                Placebo ORKAMBI (n=101)

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.

Click here for Important Safety Information and full Prescribing Information.

EXTENSION STUDY | BMI RESULTS THROUGH EXTENSION WEEK 96

Absolute Change From Baseline in BMI Through Extension Week 96

ORKAMBI: +1.78 kg/m² (95% CI 1.56, 1.99) change from baseline
Placebo: +2.04 kg/m² (95% CI 1.77, 2.31) change from baseline

Baseline was from Trial 3 or 4.

Please see page 14 for Limitations and Disclosures of Trials 3, 4, and the Extension Study.

IMPORTANT SAFETY INFORMATION

Drug Interactions (cont)

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.
CFQ-R Respiratory Domain score

RESULTS FOR CFQ-R RESPIRATORY DOMAIN SCORE

Trial 3: +5.4 point (95% CI 1.4, 9.4) within-group mean absolute change from baseline through Week 24

• Trial 4: +2.5 point (95% CI -0.1, 5.1) LS mean treatment difference vs placebo through Week 24.

CFQ-R Respiratory Domain score was assessed as a secondary endpoint.

• Within-group LS mean absolute change was +5.5 points (95% CI 3.4, 7.6) for ORKAMBI® (lumacaftor/ivacaftor) and +3.0 points (95% CI 1.0, 5.0) for placebo.

• Power for secondary endpoints was limited. Analysis of secondary endpoints was not adjusted for multiplicity.

• Extension Study: +7.4 point (95% CI 4.8, 10.0) increase from baseline through Extension Week 96 in the ORKAMBI®/ORKAMBI group and +6.6 point (95% CI 3.1, 10.0) increase in the placebo=ORKAMBI group.

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.

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 rhinitis.

• 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 ≥2% 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

SAFETY PROFILE 1

TRIAL 3 (OPEN-LABEL SAFETY)

• Serious adverse reactions included infective pulmonary exacerbations, ileus, and elevated liver transaminases.

• Most common adverse events (>10%) included cough, nasopharyngitis, infective pulmonary exacerbation, headache, sputum increased, abdominal pain upper, elevated alanine aminotransferase levels, abdominal pain, nausea, vomiting, fatigue, and pyrexia.

TRIAL 4 (PLACEBO CONTROLLED)

• Serious adverse reactions in the ORKAMBI group included drug interaction and obstructive airways disorder.

• Most common adverse events (≥5% for ORKAMBI and also ≥3% higher than placebo) included productive cough, nasal congestion, oropharyngeal pain, sputum increased, rhinitis, abdominal pain upper, headache, and rash.

SUMMARY OF OTHER RESULTS

LS mean absolute change from baseline

TRIAL 3 (OPEN-LABEL SAFETY)

PERCENTAGE POINTS

+2.5 (within-group) (% of the safety assessment) 1

+2.4 (within-group) (pharmacodynamic assessment) 2

SWEAT CHLORIDE

-24.8 mmol/L (within-group) 1

+0.5 mmol/L (within-group) 2

CFQ-R Respiratory Domain

+5.4 points (within-group) 2

TRIAL 4 (PLACEBO CONTROLLED)

PERCENTAGE POINTS

-1.1 (within-group) 3

+2.4 (within-group) 3

SWEAT CHLORIDE

-20.8 mmol/L (within-group) 3

+0.6 mmol/L (within-group) 3

CFQ-R Respiratory Domain

+2.5 points (within-group) 3

EXTRACTION STUDY

239 patients continued for an additional 96 weeks. See pages 12-28 for more information 4.

ADDITIONAL LIMITATIONS AND DISCLOSURES

• The Trial 4 efficacy results and the Extension Study were not included in the approved full Prescribing Information, and the FDA did not consider either study in approving ORKAMBI.

• The Extension Study may not meet the FDA definition of an adequate and well-controlled study due to its study design

• Please see page 14 for limitations and disclosures of Trials 3, 4, and the Extension Study

*The results for percent predicted FEV1, and sweat chloride are based on an uncontrolled, open-label study, and therefore, hypothesis testing cannot determine whether within-arm changes were due to drug effect. There was no direct correlation between decrease in sweat chloride levels and improvement in lung function (percent predicted FEV1). 1

*Baseline is defined as the average of the measurements at screening and on Day 1 (predose) in Trial 3. 10

*Power for secondary endpoints in Trial 4, including key secondary endpoints, was limited. Analysis of secondary endpoints was not adjusted for multiplicity. 12

Click here for Important Safety Information and full Prescribing Information.
**ORKAMBI® (lumacaftor/ivacaftor) studied in patients age 12 years and older**

**TRIAL 1**
- Phase 3, Randomized, Double-blind
- 24-WEEK TREATMENT

- ORKAMBI
  - lumacaftor 400 mg/ivacaftor 250 mg q12h (n=182)

- Placebo
  - (n=184)

**TRIAL 2**
- Phase 3, Randomized, Double-blind
- 24-WEEK TREATMENT

- ORKAMBI
  - lumacaftor 400 mg/ivacaftor 250 mg q12h (n=187)

- Placebo
  - (n=187)

- All patients remained on currently prescribed CF therapies

**PRIMARY ENDPOINT**
- Absolute change in percent predicted FEV1 from baseline at Week 24

**SELECTED SECONDARY ENDPOINTS**
- Listed in order evaluated by statistical analyses hierarchy:
  - Relative change in percent predicted FEV1 at Week 24 (percentage)
  - Absolute change in BMI at Week 24 (kg/m2)
  - Absolute change in respiratory CFQ-R domain score at Week 24 (points)
  - Proportion of patients with ≥5% relative change in percent predicted FEV1

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

**KEY INCLUSION CRITERIA**
- ≥12 years old
- Confirmed CF diagnosis
- Clinically stable
- F508del homozygous
- ppFEV1, 40 to 90 at screening

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

**TRIAL 1**
- Placebo
  - (n=184)
- ORKAMBI
  - (n=182)

**TRIAL 2**
- Placebo
  - (n=187)
- ORKAMBI
  - (n=187)

**POOLED**
- Placebo
  - (n=371)
- ORKAMBI
  - (n=369)

**PRIMARY ENDPOINT**
- Absolute change in percent predicted FEV1 at Week 24 (percentage point)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td>2.7 (1.7, 3.8) - 0.8 (0.7, 3.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.9 (1.7, 4.1) - 0.8 (0.7, 3.1)</td>
</tr>
</tbody>
</table>

**SELECTED SECONDARY ENDPOINT**
- Relative change in percent predicted FEV1 at Week 24 (percentage)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td>1.9 (1.7, 2.2) - 0.2 (0.1, 0.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.0 (1.7, 2.3) - 0.2 (0.1, 0.3)</td>
</tr>
</tbody>
</table>

**POOLED ENDPOINT**
- Relative change in percent predicted FEV1 at Week 24 (percentage)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative change in percent predicted FEV1 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td>2.1 (1.5, 2.8) - 0.3 (0.2, 0.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.2 (1.6, 2.9) - 0.3 (0.2, 0.4)</td>
</tr>
</tbody>
</table>

**POOLED ENDPOINT**
- Absolute change in BMI at Week 24 (kg/m2)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Absolute change in BMI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td>0.5 (0.2, 0.7) - 0.1 (0.0, 0.2)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2 (0.0, 0.4) - 0.1 (0.0, 0.2)</td>
</tr>
</tbody>
</table>

**POOLED ENDPOINT**
- Absolute change in respiratory CFQ-R domain score at Week 24 (points)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Absolute change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td>1.5 (1.2, 1.8) - 0.3 (0.2, 0.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.7 (1.4, 2.0) - 0.3 (0.2, 0.5)</td>
</tr>
</tbody>
</table>

**POOLED ENDPOINT**
- Proportion of patients with ≥5% relative change in percent predicted FEV1 at Week 24 (percentage)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
<td>37% (33%, 41%) - 22% (18%, 26%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>39% (35%, 43%) - 22% (18%, 26%)</td>
</tr>
</tbody>
</table>

**POOLED ENDPOINT**
- Number of pulmonary exacerbations through Week 24 (rate per 48 weeks)

<table>
<thead>
<tr>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORKAMBI</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

*As assessed as the average of the treatment effects at the Week 16 and Week 24 time points.

**IMPORTANCE OF 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

**IMPORTANT SAFETY INFORMATION**

- In each trial, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs placebo. For an endpoint to be significant, both it and all previous tests had to achieve P≤0.025.
- 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 pre-specified and did not correct for multiple comparisons

**Click here for Important Safety Information and full Prescribing Information.**
The overall safety profile of ORKAMBI® (LUMACAFTOR/IVACAFTOR) is based on pooled data from trials 1 and 2.

Discontinuations due to adverse events
- ORKAMBI 5%; placebo 2%

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 those below. These occurred in 1% or less of patients:
  - Pneumonia
  - Hemoptysis
  - Increased blood creatine phosphokinase
  - Cough
  - Transaminase elevations

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® (lumacaftor/ivacaftor) and those who received placebo.
  - Of these three, one had elevated transaminases (>3 x ULN) associated with bilirubin elevation >2 x ULN.
  - Following discontinuation or interruption of ORKAMBI, transaminases decreased to <3 x ULN.
  - Among six patients with pre-existing 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 abnormality) was more common in patients treated with ORKAMBI (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 pre-treatment FEV1.

Most respiratory symptom-related adverse events occurred within the first week of treatment and resolved within 2 weeks.
- During a 24-week, open-label, Phase 3b clinical trial in 46 patients aged 12 years and older (Trial 5) with advanced lung disease (ppFEV1 <40) [mean ppFEV1 29.1 at baseline (range: 18.3 to 42.0)], the incidence of respiratory symptom-related adverse reactions was 65%.\(^1\)

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%, respectively, in patients treated with ORKAMBI compared with 1.6% and 0.5% in patients who received placebo.
### ADVERSE REACTIONS IN ≥5% OF PATIENTS TREATED WITH ORKAMBI® (lumacaftor/ivacaftor) AND AT A HIGHER RATE THAN PLACEBO

<table>
<thead>
<tr>
<th>Adverse Reaction (Preferred Term)</th>
<th>ORKAMBI N=369 (%)</th>
<th>Placebo N=370 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>48 (13)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>48 (13)</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>46 (13)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45 (12)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>37 (10)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34 (9)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Respiration abnormal*</td>
<td>32 (9)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>27 (7)</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>25 (7)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>24 (7)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>21 (6)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Influenza</td>
<td>19 (5)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

*Reported as chest tightness.21

### Trials 1 and 2 in patients age 12 years and older

Common adverse reactions

Click here for Important Safety Information and full Prescribing Information.
Recommended dose for ORKAMBI® (lumacaftor/ivacaftor)

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Granules</td>
<td>For patients age 2 to &lt;6 years, the recommended dose is weight based</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
</tr>
</tbody>
</table>

- <14 kg: One packet containing lumacaftor 100 mg/ivacaftor 125 mg every 12 hours
- ≥14 kg: One packet containing lumacaftor 150 mg/ivacaftor 188 mg every 12 hours

For patients age 6 years and older
- Age 6-11 years: 2 tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours
- Age 12+ years: 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours

ORKAMBI oral granules and tablets should be taken with fat-containing food

Missed dose of oral granules or tablets
- 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

Click here for Important Safety Information and full Prescribing Information.
How to administer ORKAMBI® (lumacaftor/ivacaftor) oral granules

PREPARATION

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

Examples of soft foods or liquids include:
- Pureed fruits or apple sauce
- Flavored yogurt or pudding
- Milk or juice
- Examples of fat-containing foods include:
  - Butter
  - Eggs
  - Cheese pizza
  - Whole-milk dairy products (e.g., whole milk, cheese, and yogurt)
- Examples of soft foods or liquids include:
  - Avocado
  - Nuts
  - Whole-milk dairy products (e.g., whole milk, cheese, and yogurt)

ADMINISTRATION

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

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
- Nuts
- Peanut butter
- Cheese pizza
- Whole-milk dairy products (e.g., whole milk, cheese, and yogurt)

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

PALATABILITY OF ORKAMBI ORAL GRANULES

- 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.
ORKAMBI safety profile in patients age 2 years and older

12+
SAFETY PROFILE

1108 PATIENTS AGE 12 YEARS AND OLDER WERE STUDIED IN TRIALS 1 AND 2
- Serious adverse reactions in Trials 1 and 2, 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

6-11
SAFETY PROFILE

262 PATIENTS AGE 6 THROUGH 11 YEARS WERE STUDIED IN TRIALS 3 AND 4
- The safety profile of ORKAMBI in children 6 through 11 years of age was similar to that in patients 12 years and older
- 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

2-5
SAFETY (PRIMARY ENDPOINT)

60 PATIENTS AGE 2 THROUGH 5 YEARS WERE STUDIED IN TRIAL 6 (OPEN-LABEL)
- The safety profile was similar to that in patients aged 6 years and older

Please see page 5 for Limitations of Trial 6 and page 14 for Limitations and Disclosures of Trials 3 and 4

Click here for Important Safety Information and full Prescribing Information.