Delivering KALYDECO® (ivacaftor) to patients as young as 6 months

An overview of clinical trial data in patients with cystic fibrosis (CF) age 6 months and older with ivacaftor-responsive CFTR mutations

Indications and Usage

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Please click for Important Safety Information and full Prescribing Information.
KALYDECO® (ivacaftor) Important Safety Information

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been reported in patients with CF receiving KALYDECO. Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. It is recommended that ALT and AST be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered.

- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing.

Concomitant Use With CYP3A Inducers

- Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort is not recommended.

Cataracts

- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment.

Pediatric Use

- The safety and efficacy of KALYDECO in patients with CF younger than 6 months of age have not been studied. The use of KALYDECO in children under the age of 6 months is not recommended.

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in patients treated with KALYDECO included abdominal pain, increased hepatic enzymes, and hypoglycemia.

Most Common Adverse Reactions

- The most common adverse reactions in patients with a G551D mutation in the CFTR gene (Trials 1 and 2) with an incidence of ≥8% and at a higher incidence for patients treated with KALYDECO (N=109) than for placebo (N=104) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.

- The safety profiles for patients with additional approved mutations enrolled in Trials 4, 5, and 7; and for patients ages 2 to less than 6 years enrolled in Trial 6; and for patients aged 6 months to less than 24 months enrolled in Trial 8; were similar to that observed in Trials 1 and 2.

Indications and Usage

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Prevalence of CFTR mutations

- Overall, KALYDECO is indicated for 38 CFTR mutations, which represent approximately 15% of the CF population in the United States.

Please click to see full Prescribing Information.

KALYDECO® (ivacaftor) targets the underlying cause of CF in patients age 6 months and older who have ivacaftor-responsive CFTR mutations

<table>
<thead>
<tr>
<th>CFTR MUTATIONS RESPONSIVE TO KALYDECO BASED ON CLINICAL AND/OR IN VITRO DATA</th>
<th>Data Source</th>
</tr>
</thead>
</table>
| A1067T c.3195G>A | 3272-26A>G | c.3195G>A
| A1067V c.3195G>C | 3272-26A>G | c.3195G>C
| A1067T c.3195G>A | 3272-26A>G | c.3195G>A
| A1067V c.3195G>C | 3272-26A>G | c.3195G>C
| A455E c.1364A>C | 3849-10b:c>T | c.1364A>C
| A455E c.1364A>G | 3849-10b:c>T | c.1364A>G
| D110E c.330C>A | 3849-10b:c>T | c.330C>A
| D110E c.330C>G | 3849-10b:c>T | c.330C>G
| D110E c.330C>A | 3849-10b:c>T | c.330C>A
| D110E c.330C>G | 3849-10b:c>T | c.330C>G
| D110H c.3290C>T | 3849-10b:c>T | c.3290C>T
| D110H c.3290C>G | 3849-10b:c>T | c.3290C>G
| D110H c.3290C>T | 3849-10b:c>T | c.3290C>T
| D110H c.3290C>G | 3849-10b:c>T | c.3290C>G
| D1152H c.3454G>C | 711+3A>G | c.3454G>C
| D1152H c.3454G>T | 711+3A>G | c.3454G>T
| D1152H c.3454G>C | 711+3A>G | c.3454G>C
| D1152H c.3454G>T | 711+3A>G | c.3454G>T
| D1270N c.3803G>A | 2789+5G>A | c.3803G>A
| D1270N c.3803G>G | 2789+5G>A | c.3803G>G
| D1270N c.3803G>A | 2789+5G>A | c.3803G>A
| D1270N c.3803G>G | 2789+5G>A | c.3803G>G
| F1021V c.3066A>G | 1-3 | c.3066A>G
| F1021V c.3066A>T | 1-3 | c.3066A>T
| F1021V c.3066A>G | 1-3 | c.3066A>G
| F1021V c.3066A>T | 1-3 | c.3066A>T
| F1052I c.3154T>G | 1-3 | c.3154T>G
| F1052I c.3154T>A | 1-3 | c.3154T>A
| F1052I c.3154T>G | 1-3 | c.3154T>G
| F1052I c.3154T>A | 1-3 | c.3154T>A
| G1246E c.3716G>A | 1-3 | c.3716G>A
| G1246E c.3716G>T | 1-3 | c.3716G>T
| G1246E c.3716G>A | 1-3 | c.3716G>A
| G1246E c.3716G>T | 1-3 | c.3716G>T
| L2854P c.8558G>A | 1-3 | c.8558G>A
| L2854P c.8558G>T | 1-3 | c.8558G>T
| L2854P c.8558G>A | 1-3 | c.8558G>A
| L2854P c.8558G>T | 1-3 | c.8558G>T
| N3258S c.9774G>A | 1-3 | c.9774G>A
| N3258S c.9774G>T | 1-3 | c.9774G>T
| N3258S c.9774G>A | 1-3 | c.9774G>A
| N3258S c.9774G>T | 1-3 | c.9774G>T
| P6702I c.19909G>A | 1-3 | c.19909G>A
| P6702I c.19909G>T | 1-3 | c.19909G>T
| P6702I c.19909G>A | 1-3 | c.19909G>A
| P6702I c.19909G>T | 1-3 | c.19909G>T
| P6702S c.19908G>A | 1-3 | c.19908G>A
| P6702S c.19908G>T | 1-3 | c.19908G>T
| P6702S c.19908G>A | 1-3 | c.19908G>A
| P6702S c.19908G>T | 1-3 | c.19908G>T
| P6702S c.19908G>A | 1-3 | c.19908G>A
| P6702S c.19908G>T | 1-3 | c.19908G>T
| R1172H c.3496G>A | 1-3 | c.3496G>A
| R1172H c.3496G>T | 1-3 | c.3496G>T
| R1172H c.3496G>A | 1-3 | c.3496G>A
| R1172H c.3496G>T | 1-3 | c.3496G>T
| S549R c.1645G>A | 1-3 | c.1645G>A
| S549R c.1645G>T | 1-3 | c.1645G>T
| S549R c.1645G>A | 1-3 | c.1645G>A
| S549R c.1645G>T | 1-3 | c.1645G>T

P508del and 26 other mutations are considered not responsive to ivacaftor (see full Prescribing Information for complete listing).
KALYDECO® (ivacaftor): Overview of clinical trial experience

**Mutations Eligible for Study**

- Mutations in bold were enrolled.
- G551D, G1244E, G1349D, G718R, G551S, R117H, R384Q,
  or S454R.
- G551D.
- G1244E, G1349D, G718R, G551S, S549N, or S454R.
- G551D, S1251N, S1255P, S549N, or S549R.
- G551D.

**Required ppFEV1 AT SCREENING**

- n/a
- 40-105
- 40-90
- 40-90

**Key exclusion criteria for all studies included infection with Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus, and abnormal liver function. In Trials 1-5, abnormal liver function was defined as 3 or more liver function tests (ALT, AST, ALP, GGT, total bilirubin) ≥3 x the upper limit of normal (ULN). In Trial 6, it was defined as liver function tests ≥2 x ULN. In Trial 7, it was defined as ≥4 x ULN. Patients with the R117H mutation could not be established.

**Dosing**

- Patients 7 kg to <14 kg: One 50 mg packet of oral granules every 12 hours
- Patients ≥14 kg: One 75 mg packet of oral granules every 12 hours

**Clinical Trials Overview**

- **TRIAL 1** (KONNECTION) pages 14-16
- **TRIAL 2** (KONDUCTION) pages 10-13
- **TRIAL 3** (ARRIVAL) pages 6-9
- **TRIAL 4** (Part 1) 8-week, randomized, double-blind, crossover efficacy and safety study (Part 1), with a 16-week open-label extension (Part 2)
- **TRIAL 4** (Part 2) 8-week, open-label safety study
- **TRIAL 5** (KONDUCT) pages 16-17
- **TRIAL 6** (KONNECT) pages 10-13
- **TRIAL 7** (KONYX) pages 20-21

**Please click to see Important Safety Information and full Prescribing Information.**

*Based on the clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the G9V/YR mutation could not be established.

**Please click to see Important Safety Information and full Prescribing Information.**
### Trial Design

- **Trial 8** was a Phase 3, 24-week, open-label, 2-part study of KALYDECO that included the following cohorts of patients with CF: Patients age 6 to <12 months (N=11) and patients age 12 to <24 months (N=19).1,5-7
- Patients were eligible to enroll in this study if they had a G551D, G1244E, G1349D, G178R, G551S, R117H, a S1251N, S1255P, S549N, or S549R mutation.1-7
- **6 to <12 months cohort:** Enrolled patients had either a G551D mutation (n=10) or a G178R mutation (n=1).7
- **12 to <24 months cohort:** Enrolled patients had the G551D mutation (n=16), S549N mutation (n=2), or G178R mutation (n=1).5

#### Primary endpoint: Safety, assessed by adverse events and clinical laboratory assessments.5,7

#### Secondary endpoints: Absolute change from baseline in sweat chloride concentration at 24 weeks.5,7

### Trial 8 limitations

- The study was open label and not placebo controlled; therefore, causality cannot be attributed to KALYDECO.5,7
- All patients in the study knew they were on active drug, which may have introduced bias related to awareness of treatment.

### Discontinuations and serious adverse events

- **6 to <12 month cohort:**
  - There was 1 treatment interruption and no permanent discontinuations due to adverse events.
  - Serious adverse events included viral respiratory tract infection (1), viral rash (1), and cough (1).
- **12 to <24 month cohort:**
  - 1 patient discontinued due to withdrawal of consent.
  - 4 serious adverse events occurred in 2 patients:
    - 1 patient had constipation, distal intestinal obstruction syndrome (DIOS), and eczema herpeticum.
    - 1 patient had persistent cough.

The serious adverse event of constipation was considered possibly related to ivacaftor by the investigator. All other serious adverse events were considered unrelated or unlikely to be related to ivacaftor.1

### Transaminase elevations

#### TRANSMINASE ELEVATIONS1

<table>
<thead>
<tr>
<th>ELEVATED ALT OR AST</th>
<th>6 TO &lt;12 MONTH COHORT</th>
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<tr>
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ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

- No patients in either cohort had elevations in total bilirubin, or discontinued ivacaftor treatment due to transaminase elevations.
- **6 to <12 month cohort:** During the course of this study, no patient interrupted treatment because of adverse events of elevated liver function tests:
  - On the last day of the study, 1 patient had an LFT elevation that resulted in subsequent treatment interruption.
- **12 to <24 month cohort:** 2 patients had study drug interrupted because of adverse events of elevated liver function tests:
  - 1 patient had adverse events of ALT increased and AST increased that led to study drug interruption.
  - 1 patient had adverse events of ALT increased, AST increased, and GGT increased that led to study drug interruption.
  - Both resumed treatment following a period of study drug interruption with no further elevations.

### IMPORTANT SAFETY INFORMATION

#### Transaminase (ALT or AST) Elevations

- Elevated transaminases have been reported in patients with CF receiving KALYDECO® (ivacaftor). Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. It is recommended that ALT and AST be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered.
- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing.

### Incidence of Transaminase Elevations

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Reduction in sweat chloride from baseline with KALYDECO® (ivacaftor): Patients age 6 to less than 12 months

- In the 6 to <12 month cohort (n=6), the mean absolute change from baseline in sweat chloride was -58.6 mmol/L (95% CI: -75.9, -41.3) at Week 24 (secondary endpoint). The reduction in sweat chloride levels was statistically significant compared to baseline.
- There was no direct correlation between decrease in sweat chloride levels and improvement in lung function (FEV1).

The safety and efficacy of KALYDECO in patients with CF younger than 6 months of age have not been established. The use of KALYDECO in children under the age of 6 months is not recommended.

**IMPORTANT SAFETY INFORMATION**

**Concomitant Use With CYP3A Inducers**
- Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort is not recommended.

**Cataracts**
- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment.

**IMPORTANT SAFETY INFORMATION**

Please click to see Important Safety Information and full Prescribing Information.
TRIAL 6 (KIWI): Patients with CF age 2 to less than 6 years
KALYDECO® (ivacaftor): Safety consistent with patients age 6 years and older

**Trial Design**
- Trial 6 was a 24-week, open-label trial (N=34) evaluating safety, pharmacokinetics, and pharmacodynamics in patients with CF age 2 to less than 6 years (mean age: 3 years). Patients were eligible if they had either a G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation.
- Of enrolled patients, 32 had either a G551D (n=32) or a S549N (n=2) mutation.
- Patients received KALYDECO every 12 hours with fat-containing food, in addition to their prescribed CF therapies, based on weight: 7 kg to <14 kg: One 50 mg packet of oral granules; ≥14 kg to <25 kg: One 75 mg packet of oral granules.

**Primary outcome:** Safety, assessed by adverse events and clinical laboratory assessments.

**Select secondary outcome measure:** Absolute change from baseline in sweat chloride concentration at 24 weeks.

**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.

**Safety results and pharmacokinetics were similar to older patients**
- The safety profile for patients in Trial 6, including type and frequency of adverse reactions, was similar to that observed in Trials 1 and 2.
- Transaminase elevations were more common in patients who had abnormal transaminases at baseline.
- The incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of KALYDECO dosing. KALYDECO was permanently discontinued in 1 patient.
- KALYDECO oral granules (2 x 75 mg) had similar bioavailability as the 150 mg tablet when given with fat-containing food.

**The efficacy of KALYDECO in patients 2 to less than 6 years was extrapolated from patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and children 2 to less than 6 years of age.**

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**Reduction in sweat chloride from baseline (pharmacodynamic measure) with KALYDECO® (ivacaftor)**

**Mean sweat chloride concentrations by visit**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean (+/-SD) (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=30)</td>
<td>115.1 (±23.5)</td>
</tr>
<tr>
<td>Wk 2 (n=29)</td>
<td>71.6 (±15.2)</td>
</tr>
<tr>
<td>Wk 8 (n=28)</td>
<td>60.2 (±15.3)</td>
</tr>
<tr>
<td>Wk 16 (n=28)</td>
<td>54.0 (±14.1)</td>
</tr>
<tr>
<td>Wk 24 (n=28)</td>
<td>50.0 (±13.1)</td>
</tr>
</tbody>
</table>

The mean absolute change from baseline in sweat chloride for patients age 2 to less than 6 years (N=34) was -45 mmol/L (95% CI: -53.0, -38.0) through Week 24 (secondary endpoint).

**Important Safety Information**

**Pediatric Use**
- The safety and efficacy of KALYDECO in patients with CF younger than 6 months of age have not been studied. The use of KALYDECO in children under the age of 6 months is not recommended.
TRIAL 2 (ENVISION): Patients with CF, ages 6 to 11 with a G551D mutation
KALYDECO® (ivacaftor): Efficacy results include significant improvement in lung function

Trial Design
- Trial 2 was a 48-week, Phase 3, randomized, double-blind, placebo-controlled trial (N=52) in patients with CF age 6 to 11 years (mean age: 9 years) and a G551D mutation
- Patients had to have FEV1 40%-105% predicted at screening [mean FEV1: 84% predicted at baseline (range: 44%-134%)]
- Patients received KALYDECO 150 mg or placebo every 12 hours with fat-containing food, in addition to their prescribed CF therapies. Use of hypertonic saline was not permitted

Primary endpoint: Improvement in lung function as determined by the mean absolute change from baseline in ppFEV1, through Week 24

Other efficacy endpoints: Absolute change in ppFEV1, through Week 48, improvement from baseline in CFO-R Respiratory Domain score through Weeks 24 and 48, absolute change from baseline in body weight at Weeks 24 and 48, and absolute change from baseline in sweat chloride concentration through Weeks 24 and 48

Improvements in ppFEV1 vs placebo were seen at the first post-baseline visit and persisted through 48 weeks

Additional efficacy endpoints1

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment difference through:</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 weeks*</td>
<td>48 weeks*</td>
</tr>
<tr>
<td>CFO-R RESPIRATORY DOMAIN SCORE</td>
<td>+6.1 points (95% CI: -1.4, 13.5; not statistically significant)</td>
</tr>
<tr>
<td>BODY WEIGHT</td>
<td>+1.9 kg (95% CI: 0.9, 2.9; P=0.0004)</td>
</tr>
<tr>
<td>SWEAT CHLORIDE (pharmacodynamic measure)</td>
<td>-54 mmol/L (95% CI: -62, -47; P&lt;0.0001)</td>
</tr>
</tbody>
</table>

*Treatment difference = effect of KALYDECO – effect of placebo.

Time to first pulmonary exacerbation was not analyzed in Trial 2 due to low incidence of events.

IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions
- Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in patients treated with KALYDECO® (ivacaftor) included abdominal pain, increased hepatic enzymes, and hypoglycemia

Most Common Adverse Reactions
- The most common adverse reactions in patients with a G551D mutation in the CFTR gene (Trials 1 and 2) with an incidence of >8% and at a higher incidence for patients treated with KALYDECO (N=109) than for placebo (N=104) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness
- The safety profiles for patients with additional approved mutations enrolled in Trials 4, 5, and 7; and for patients ages 2 to less than 6 years enrolled in Trial 6; and for patients aged 6 months to less than 24 months enrolled in Trial 8; were similar to that observed in Trials 1 and 2

Please click to see Important Safety Information and full Prescribing Information.
TRIAL 4 (KONNECTION): Patients with CF age 6 years and older

KALYDECO® (ivacaftor): Significant improvements demonstrated for the overall population with eligible mutations

Trial Design

- Trial 4 was a Phase 3, two-part, randomized, double-blind, placebo-controlled, crossover design trial (two 8-week treatment periods separated by a 4- to 8-week washout period; N=39) in patients with CF age 6 years and older (mean age: 23 years)
  - Patients had either a G1244E (n=5), G1349D (n=2), G178R (n=5), G551S (n=2), G970R (n=4), S1251N (n=8), S1255P (n=2), S549N (n=6), or S549R (n=4) mutation
  - KALYDECO is not indicated for use in patients with a G970R mutation
- Patients had to have FEV1 ≥40% predicted at screening [mean FEV1 78% predicted at baseline (range: 43%-119%)]
- Patients received KALYDECO 150 mg or placebo every 12 hours with fat-containing food, in addition to their prescribed CF therapies

Primary endpoint: Improvement in lung function as determined by the mean absolute change from baseline in ppFEV1 through 8 weeks

Other endpoints: Absolute change from baseline in: BMI at 8 weeks, improvement in CFQ-R Respiratory Domain score through 8 weeks, and sweat chloride concentration through 8 weeks

Significant improvements in ppFEV1, through 8 weeks of treatment

There was a high degree of variability of responses among the 9 mutations studied

For individual mutations, mean increases in ppFEV1, ranged from +3% points to +20% points at Week 8

Based on the clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the G970R mutation could not be established

ABSOLUTE CHANGE FROM BASELINE IN ppFEV1

<table>
<thead>
<tr>
<th>Week</th>
<th>Mean Absolute Change (Percentage Points, Mean +/-SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>5.5 (+10.7% POINTS THROUGH 8 WEEKS [95% CI: 7.3, 14.1; P&lt;0.0001])</td>
</tr>
<tr>
<td>8</td>
<td>10.7</td>
</tr>
</tbody>
</table>

-10 0 5 10 15

BMI

Treatment difference at 8 weeks*

+0.66 kg/m² (95% CI: 0.34, 0.99; P=0.0001)

CFQ-R RESPIRATORY DOMAIN SCORE

Treatment difference through 8 weeks

+9.6 points (95% CI: 4.5, 14.7; P=0.0004)

SWEAT CHLORIDE (pharmacodynamic measure)

Treatment difference through 8 weeks

-49 mmol/L (95% CI: -57, -41; P=0.0001)

*Reflects results from the 1 patient with the G551S mutation with data at the 8-week time point.

See the full Prescribing Information for complete results by mutation.

IMPORTANT SAFETY INFORMATION

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been reported in patients with CF receiving KALYDECO® (ivacaftor). Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. It is recommended that ALT and AST be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered
- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing

Please click to see Important Safety Information and full Prescribing Information.
Results with KALYDECO® (ivacaftor) in patients with the R117H mutation

Trial 5 was a 24-week, Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial in patients with CF age 6 years and older (mean age: 31 years) who had an R117H mutation.

- Patients age 12 years and older had to have FEV1 40%-90% predicted at screening; patients age 6 to 11 years had to have FEV1 40%-105% predicted at screening; mean FEV1 73% predicted at baseline (range: 33%-106%) 1
- Patients received KALYDECO 150 mg or placebo every 12 hours with fat-containing food, in addition to their prescribed CF therapies
- Subgroups analyzed were based on age, lung function, and poly-T status

Primary endpoint: Improvement in lung function as determined by the mean absolute change from baseline in ppFEV1 through 24 weeks1

Other efficacy endpoints: Absolute change in BMI at Week 24, CFQ-R Respiratory Domain score through Week 24, time to first pulmonary exacerbation, and absolute change in sweat chloride from baseline through Week 24

Overall change in ppFEV1, through Week 24, 2.1 percentage points (N=69), was not statistically significant1

### Absolute Change in ppFEV1, Through Week 24 1

<table>
<thead>
<tr>
<th>Subgroup Parameter</th>
<th>Treatment Arm</th>
<th>n</th>
<th>Mean</th>
<th>Treatment Differencea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R117H—all patients</td>
<td>Placebo</td>
<td>35</td>
<td>0.5</td>
<td>2.1 (-1.1, 5.4)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>34</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Subgroup by age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-11</td>
<td>Placebo</td>
<td>8</td>
<td>3.5</td>
<td>-6.3 (-12.0, -0.7)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>9</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>12-17</td>
<td>Placebo</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>≥18</td>
<td>Placebo</td>
<td>26</td>
<td>-0.5</td>
<td>5.0 (1.1, 8.8)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>24</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Subgroup by poly-T statusc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5T</td>
<td>Placebo</td>
<td>24</td>
<td>0.7</td>
<td>5.3 (1.3, 9.3)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>14</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>7T</td>
<td>Placebo</td>
<td>5</td>
<td>-0.9</td>
<td>0.2 (-8.1, 8.5)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>11</td>
<td>-0.7</td>
<td></td>
</tr>
<tr>
<td>Subgroup by baseline FEV1% predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70%</td>
<td>Placebo</td>
<td>15</td>
<td>0.4</td>
<td>4.0 (-2.1, 10.1)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>13</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>70%-90%</td>
<td>Placebo</td>
<td>14</td>
<td>0.2</td>
<td>2.6 (-2.3, 7.5)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>14</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>Placebo</td>
<td>6</td>
<td>2.2</td>
<td>-4.3 (-9.9, 1.3)</td>
</tr>
<tr>
<td></td>
<td>KALYDECO</td>
<td>7</td>
<td>-2.1</td>
<td></td>
</tr>
</tbody>
</table>

1Treatment difference = effect of KALYDECO—in effect of placebo.1
2Poly-T status confirmed by genotyping (n=54).

### IMPORTANT SAFETY INFORMATION

Concomitant Use With CYP3A Inducers

- Use of KALYDECO® (ivacaftor) with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort is not recommended

HR, hazard ratio.

Please click to see Important Safety Information and full Prescribing Information.
TRIAL 1 (STRIVE): Patients with CF age 12 years and older with a G551D mutation
KALYDECO® (ivacaftor) achieved significant improvements across multiple clinical endpoints in patients with a G551D mutation

**Trial Design**
- Trial 1 was a 48-week, Phase 3, randomized, double-blind, placebo-controlled trial (N=161) in patients with CF age 12 years and older (mean age: 26 years) and a G551D mutation
- Patients had to have FEV1 40%-90% predicted at screening [mean FEV1 64% predicted at baseline (range: 32%-98%)]
- Patients received KALYDECO 150 mg or placebo every 12 hours with fat-containing food, in addition to their prescribed CF therapies. Use of hypertonic saline was not permitted

**Primary endpoint:** Improvement in lung function as determined by the mean absolute change from baseline in ppFEV1 through 24 weeks\(^1\)

**Other efficacy endpoints:** Absolute change in ppFEV1, through Week 48, improvement from baseline in CFQ-R Respiratory Domain score through Weeks 24 and 48, time to first pulmonary exacerbation through Weeks 24 and 48, absolute change from baseline in body weight at Weeks 24 and 48, and absolute change from baseline in sweat chloride concentration through Weeks 24 and 48\(^1\)

Significant improvements in lung function were seen through 24 weeks and persisted through 48 weeks\(^1,13,17\)

<table>
<thead>
<tr>
<th>Treatment difference through:</th>
<th>24 weeks(^a)</th>
<th>48 weeks(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFQ-R RESPIRATORY DOMAIN SCORE</td>
<td>+8.1 points (95% CI: 4.7, 11.4; P&lt;0.0001)</td>
<td>+8.6 points (95% CI: 5.3, 11.9; P&lt;0.0001)</td>
</tr>
</tbody>
</table>

**Significant changes vs placebo: +10.6 points (95% CI: 8.6, 12.6; P<0.0001) +10.5 points (95% CI: 8.5, 12.5; P<0.0001)**

**Clinical endpoints studied in Trial 1 for KALYDECO® (ivacaftor) showed significant, sustained improvements vs placebo**

**RELATIVE RISK OF PULMONARY EXACERBATION | Treatment difference through:**
- **24 weeks\(^a\)** 60% reduction (HR, 0.40; P=0.0016)
- **48 weeks\(^a\)** 54% reduction (HR, 0.46; P=0.0012)

**BODY WEIGHT | Treatment difference at:**
- **24 weeks\(^a\)** +2.8 kg (95% CI: 1.8, 3.7; P<0.0001)
- **48 weeks\(^a\)** +2.7 kg (95% CI: 1.3, 4.1; P=0.0001)

**SWEAT CHLORIDE (pharmacodynamic measure) | Treatment difference through:**
- **24 weeks\(^a\)** -48 mmol/L (95% CI: -51, -45; P<0.0001)
- **48 weeks\(^a\)** -48 mmol/L (95% CI: -51, -45; P<0.0001)

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**IMPORTANT SAFETY INFORMATION**

**Cataracts**
- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment

**Pediatric Use**
- The safety and efficacy of KALYDECO in patients with CF younger than 6 months of age have not been studied. The use of KALYDECO in children under the age of 6 months is not recommended

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Please click to see Important Safety Information and full Prescribing Information.
TRIAL 7: Patients with CF age 12 years and older with specific ivacaftor-responsive mutations KALYDECO® (ivacaftor) improved lung function vs placebo overall and across all prespecified subgroups

Trial Design
- Trial 7 was an 8-week, randomized, double-blind, placebo-controlled, 2-period, crossover design trial (N=246) in patients with CF age 12 years and older [mean age: 35 years]1,4
  - Patients were heterozygous for the F508del mutation and a second mutation predicted to be responsive to ivacaftor
  - The 5 splice mutations studied were: 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G, E831X [n=94 for KALYDECO and n=97 for placebo]
  - The 11 missense mutations studied were: A455E, D1152H, D579G, L206W, P67L, R1070W, R117C, R347H, R352Q, S945L, S977F [n=62 for KALYDECO and n=63 for placebo]

- Patients had to have FEV1 40%-90% predicted at screening [mean FEV1 62% predicted at baseline (range: 35%-94%)]1
- Patients received KALYDECO 150 mg or placebo every 12 hours with fat-containing food, in addition to their prescribed CF therapies16

Primary endpoint: Mean absolute change from baseline in ppFEV1, to the average of Weeks 4 and 8
Key secondary endpoint: Absolute change from baseline in CFQ-R Respiratory Domain score averaged at Weeks 4 and 8

Significant improvement in ppFEV1, by Day 15 maintained through 8 weeks1,18

ABSOLUTE CHANGE FROM BASELINE IN ppFEV1, AVERAGED AT WEEKS 4 AND 81,18

<table>
<thead>
<tr>
<th>Week</th>
<th>PPFEV1 (Percentage Points, LS Mean [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>4.7% (3.7, 5.8)</td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Day 15</td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission from Rowe SM et al. N Engl J Med. 2017;377(21);2024-2035.

*The complete study design and results are not reported here; only the KALYDECO and placebo groups are shown.

Improvements in ppFEV1 were observed with KALYDECO® (ivacaftor) across all prespecified subgroups vs placebo1,18,19

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treatment Differencea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4.7 (3.7, 5.8)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>8.0 (5.2, 10.7)</td>
</tr>
<tr>
<td>≥18 years</td>
<td>4.2 (3.1, 5.3)</td>
</tr>
<tr>
<td>Baseline ppFEV1</td>
<td></td>
</tr>
<tr>
<td>≥40 to &lt;70</td>
<td>4.4 (2.8, 7.0)</td>
</tr>
<tr>
<td>≥70 (KALYDECO n=50; placebo n=50)</td>
<td>4.3 (2.5, 7.1)</td>
</tr>
<tr>
<td>Mutation Group</td>
<td></td>
</tr>
<tr>
<td>The 5 splice (KALYDECO n=94; placebo n=97)</td>
<td>5.4 (4.1, 6.8)</td>
</tr>
<tr>
<td>The 11 missense (KALYDECO n=62; placebo n=63)</td>
<td>3.6 (1.8, 5.2)</td>
</tr>
</tbody>
</table>

*Additional subgroups analyzed included: region, sex, colonization of Pseudomonas aeruginosa; use of azithromycin; and use of inhaled antibiotics, bronchodilators, hypertonic saline, and corticosteroids.

*bTreatment difference = effect of KALYDECO – effect of placebo.

For individual mutations, changes in ppFEV1 varied by genotype and ranged from +2.4% points to +13.3% points; see the full Prescribing Information for results by mutation. These were ad hoc analyses

Significant improvement in CFQ-R Respiratory Domain score from baseline for KALYDECO vs placebo overall1,18
- The overall treatment difference was 9.7 points (95% CI: 7.2, 12.2; P<0.0001)
- For individual mutations, results varied by genotype and ranged from -8.3 to 44.4; see full Prescribing Information for results by mutation. These were ad hoc analyses

IMPORTANT SAFETY INFORMATION

Serious Adverse Reactions
- Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in patients treated with KALYDECO included abdominal pain, increased hepatic enzymes, and hypoglycemia

Most Common Adverse Reactions
- The most common adverse reactions in patients with a G551D mutation in the CFTR gene (Trials 1 and 2) with an incidence of ≥8% and at a higher incidence for patients treated with KALYDECO (N=109) than for placebo (N=104) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness
- The safety profiles for patients with additional approved mutations enrolled in Trials 4, 5, and 7; and for patients ages 2 to less than 6 years enrolled in Trial 8; and for patients aged 6 months to less than 24 months enrolled in Trial 8; were similar to that observed in Trials 1 and 2

Please click to see Important Safety Information and full Prescribing Information.
KALYDECO® (ivacaftor) safety profile established in clinical trials

The overall safety profile for KALYDECO is based on Trials 1, 2, and 3:

- The overall safety profile for KALYDECO is based on pooled data from 3 placebo-controlled clinical trials conducted in 353 patients age 6 years and older with CF who had a G551D mutation in the CFTR gene (Trials 1 and 2) or were homozygous for the F508del mutation (Trial 3).
- KALYDECO is not indicated in patients with CF who are homozygous for the F508del mutation.

Pooled safety data from Trials 1, 2, and 3:

- The proportion of patients who prematurely discontinued study drug due to adverse reactions was 2% for patients treated with KALYDECO and 5% for patients treated with placebo.

Most common adverse reactions in Trials 1 and 2:

- The most common adverse reactions in patients treated with KALYDECO in Trials 1, 2, and 3 (N=221) were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%).

Serious adverse reactions that occurred more frequently in patients treated with KALYDECO included:

- Abdominal pain
- Increased hepatic enzymes
- Hypoglycemia

Most common adverse reactions in Trials 1 and 2:

- The overall safety profile for the patients with CF enrolled in the other clinical trials (Trials 3-8) was similar to that observed in the 48-week placebo-controlled trials (Trials 1 and 2).

Please click to see Important Safety Information and full Prescribing Information.
Recommended dose for KALYDECO® (ivacaftor)

**Recommended dose**

For patients age 6 months to <6 years, the recommended dose is weight-based:

- **5 kg to <7 kg**: One 25 mg packet every 12 hours
- **7 kg to <14 kg**: One 50 mg packet every 12 hours
- **≥14 kg**: One 75 mg packet every 12 hours

For patients age 6 years and older:

- One 150 mg tablet every 12 hours

 Patients should continue taking all of their prescribed CF therapies with KALYDECO®

- The safety and efficacy of KALYDECO for pediatric patients less than 6 months of age has not been established. The use of KALYDECO (oral granules) in children under the age of 6 months is not recommended.
- See page 26 for more information on administration of KALYDECO oral granules.

Dosage adjustments for KALYDECO® (ivacaftor)

**HEPATIC IMPAIRMENT**

- **Severe** (Child-Pugh Class C):
  - One dose once daily, or less

- **Moderate** (Child-Pugh Class B):
  - One dose once daily

- **Mild** (Child-Pugh Class A):
  - No dose adjustment required

**CYP3A**

- Co-administration with strong CYP3A inhibitors:
  - One dose twice a week
- Co-administration with moderate CYP3A inhibitors:
  - One dose once daily

**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.
How to administer KALYDECO® (ivacaftor) oral granules: 3 steps

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

EXAMPLES OF SOFT FOODS OR LIQUIDS INCLUDE:
- Pureed fruits, vegetables, or applesauce
- Milk or juice
- Breast milk, prepared infant formula
- Yogurt, water

2 ADMINISTRATION
- After mixing, caregiver should give 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 after the oral granules dose

EXAMPLES OF FAT-CONTAINING FOODS INCLUDE:
- Avocado
- Cheese pizza
- Peanut butter
- Butter
- Cheese
- Whole-milk dairy products (e.g., whole milk, cheese, and yogurt)

Food containing grapefruit or Seville oranges may increase exposure of ivacaftor, and should be avoided during treatment with KALYDECO®


Please click to see Important Safety Information and full Prescribing Information.
KALYDECO® (ivacaftor): Studied in patients with CF age 6 months and older with responsive CFTR mutations

KALYDECO has an established safety profile demonstrated in placebo-controlled clinical trials

- Serious adverse reactions that occurred more frequently in patients treated with KALYDECO included abdominal pain, increased hepatic enzymes, and hypoglycemia
- The most common adverse reactions in patients treated with KALYDECO in Trials 1, 2, and 3 (N=221) were headache, upper respiratory tract infection, nasal congestion, nausea, rash, rhinitis, dizziness, arthralgia, and bacteria in sputum

Indications and Usage

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Remember to also consider:

- Transaminases (See page 2)
- CYP3A Inducers (See page 2)
- Cataracts (See page 2)

Please click to see Important Safety Information and full Prescribing Information.