CFTR-TARGETED THERAPY FOR PATIENTS WITH CF WHO HAVE RESPONSIVE MUTATIONS

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.

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 for SYMDEKO.

People with CF pictured may or may not be taking SYMDEKO.
CF is a genetic, systemic disease that results in progressive lung disease and can ultimately lead to pulmonary failure.1,2

CF causes an average annual decline of 1-3% in lung function.1,4

Estimated Decline in Lung Function in Patients With CF With Certain Genotypes From 2006 to 2014 Based on Analysis of the CFFPR6

- By age 12, ≥30% of patients will experience ≥1 pulmonary exacerbations per year2
- In patients with CF, ≥25% of FEV1 decline is associated with pulmonary exacerbations5,6
- Pulmonary exacerbations may have devastating effects on patients, including being associated with subsequent reductions in lung function, which may be permanent.5,7

Pulmonary exacerbations significantly contribute to lung function decline.5,7

Study overview: Retrospective analysis of patients in the US CFFPR from 2006 to 2014. Objective was to characterize and compare rate of decline of ppFEV1 in patients heterozygous for F508del with patients heterozygous for F508del and a mutation associated with residual CFTR activity.

Limitations and Disclosures: The severity of disease in patients with CF and a mutation associated with residual CFTR activity is highly variable. Analysis of patients with genotypes with residual CFTR activity only included patients heterozygous for F508del and may not be applicable to other genotypes.

1. This was a retrospective cohort study of lung function decline in pediatric and adult patients with CF. The data were extracted from the Toronto CF Database, and from 1997 to 2008, 851 patients were included and 415 patients had at least 1 pulmonary exacerbation per year.2

2. In patients with CF, 52% of FEV1 decline is associated with pulmonary exacerbations.1,2

3. 25% of patients do not recover to baseline FEV1 within 3 months after treatment.6,8

4. Pulmonary exacerbations may have devastating effects on patients, including being associated with subsequent reductions in lung function, which may be permanent.5,7

5. A cohort study of patients age 16 years from the CFFPR. The objective of the study was to determine the proportion of patients who do not recover to previous baseline pulmonary function levels after pulmonary exacerbation. The study included those who were treated for at least 1 pulmonary exacerbation with antibiotics between January 1, 2003 and December 1, 2006. One randomly selected pulmonary exacerbation was analyzed per patient.1

6. CFFPR, Cystic Fibrosis Foundation Patient Registry; FEV1, forced expiratory volume in 1 second; ppFEV1, percent predicted forced expiratory volume in 1 second; SE, standard error.

CF causes an average annual decline of 1-3% in lung function.1,4

Even patients with CF who have normal ppFEV1 may have evidence of structural lung damage.8,9

HRCT scans below show evidence of pulmonary abnormalities in 2 patients with high ppFEV1.10,11

30-YEAR-OLD patient with ppFEV1 of 94%.11

13-YEAR-OLD patient with ppFEV1 of 96%.10,8

Case scenario of a patient from a retrospective study of 39 patients studied at the Irish National Referral Centre for Adult CF who received 2 HRCT scans >18 months apart. The mean age was 22 years, and all patients had documented clinical, radiologic, or genotypic features of CF as well as sweat sodium and chloride >60 mmol/L. Image shows a patient at age 13 with ppFEV1 of 96%; HRCT shows moderate bronchiectasis (straight arrow), peribronchial wall thickening (curved arrow), and an apical bulla (arrowhead).11

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HRCT, high-resolution computed tomography; PFT, pulmonary function test.
**indications and usage**

SYMDEKO® (tezacaftor/ivacaftor) is indicated for the treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. 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.

**important safety information**

- **Transaminase (ALT or AST) Elevations**
  - Elevated transaminases have been observed in patients with CF treated with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered.
  - Dosing should be interrupted in patients with significant elevations of transaminases (e.g., ALT or AST >5x upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN) and laboratory tests should be closely followed until abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment.

- **Concomitant Use With CYP3A Inducers**
  - Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO 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 have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO.

- **Pediatric Use**
  - The safety and efficacy of SYMDEKO in patients with CF younger than 6 years of age have not been studied.

- **Serious Adverse Reactions**
  - Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs. 0 placebo patients.

- **Most Common Adverse Reactions**
  - The most common adverse reactions in Trials 1 and 3 occurring in ≥3% of patients treated with SYMDEKO (N=334) and at a higher rate than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness.
  - The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3.

**adding tezacaftor to ivacaftor targets specific CFTR protein defects, increasing total CFTR activity**

Together, tezacaftor and ivacaftor improve CFTR activity.

**transmembrane conductance regulator (CFTR) gene**

**chloride ions**

**CFTR protein**

**outside of the cell**

**inside of the cell**

**important safety information**

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  - The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3.
A CF treatment for indicated patients not currently on a CFTR modulator or those considering another option

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) targets CFTR protein defects in a diverse range of genotypes

Transaminase (ALT or AST) Elevations
- Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered.
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Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.
TRIAL 4

Patients age 6 through 11 years with CF homozygous for F508del or heterozygous for F508del and a mutation predicted to be responsive to tezacaftor/ivacaftor

Study Design
Phase 3, 24-week, open-label, multicenter study evaluating the pharmacokinetics, safety, and tolerability of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor):12,15
- Patients (N=70) received tezacaftor/ivacaftor and ivacaftor. Dosage was based on weight12,15:
  - <40 kg (n=62): tezacaftor/ivacaftor 50 mg/75 mg qd + ivacaftor 75 mg qd approximately 12 hours apart15
  - ≥40 kg (n=8): tezacaftor/ivacaftor 100 mg/150 mg qd + ivacaftor 150 mg qd approximately 12 hours apart15
- Trial 4 was an open-label study with no placebo comparator arm15
- Trial 4 was conducted using a weight-based dosing regimen that differs from the FDA-approved dosing regimen for patients age 6 through 11 years. See Limitations and Disclosures on next page for FDA-approved dosing and administration details

Study Population
- Selected inclusion criteria
  - Confirmed CF diagnosis and clinically stable16
  - Patients between 6 and 11 years of age (mean age 8.1 years)15,16
  - Patients homozygous for F508del (n=61) or with one copy of the F508del mutation and one copy of a mutation predicted to be responsive to tezacaftor/ivacaftor (n=9). Indicated mutations that were enrolled included F508del plus the following: F508del, R352Q, 3272-26A→G, 2789+5G→A, ΔF508, IVS5+1G, and D579G15,16
  - Percent predicted FEV1 (ppFEV1) ≥40% at screening (mean baseline ppFEV1, 91.1, range: 63.4 to 118.0)16,17
  - Body weight at screening ≥15 kg without shoes (mean baseline weight 30.7 kg, range: 19.1 kg to 58.0 kg)16,17
- Selected exclusion criteria
  - Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN), or AST or ALT ≥5 x ULN15
  - History of colonization with organisms associated with a more rapid decline in pulmonary status, such as Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus15,16

TRIAL 4 LIMITATIONS AND DISCLOSURES
• Enrollment was limited to only those patients who met strict inclusion criteria and elected to enroll
• The study was open label and not placebo controlled; therefore, causality cannot be attributed to SYMDEKO

TRIAL 4

Patients age 6 through 11 years with CF homozygous for F508del or heterozygous for F508del and a mutation predicted to be responsive to tezacaftor/ivacaftor (cont)

Endpoints
• Primary endpoint (please see pages 10 and 11):15
  - Safety and tolerability of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) through Week 24 as determined by adverse events and clinical and laboratory assessments
• Select secondary endpoints (please see pages 12 and 13):15
  - Absolute change in sweat chloride from baseline through Week 4 and Week 24
  - Absolute change in ppFEV1 from baseline through Week 4 and Week 24
  - Relative change in ppFEV1 from baseline through Week 24
  - Absolute change in BMI and BMI-for-age z-score from baseline at Week 24
  - Absolute change in CFQ-R Respiratory Domain score (child version) from baseline through Week 24

• Patients who completed the 24-week study were offered the opportunity to enroll in an extension study. Patients who prematurely discontinued study drug treatment were not eligible to roll over into the extension study15,17

ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase; IV, intravenous; qd, once a day.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Safety results through Week 24 were similar to those observed in patients age 12 years and older\textsuperscript{12}

- Trial 4 was conducted using a weight-based dosing regimen that differs from the FDA-approved dosing regimen for patients age 6 through 11 years. See FDA-approved dosing and administration details on page 39 and limitations and disclosures on page 9.

### Trial 4 primary endpoint

**Discontinuations\textsuperscript{15}\textsuperscript{17}**

- The proportion of patients who discontinued study drug due to adverse events was:
  - **1.4% OF PATIENTS TREATED WITH SYMDEKO\textsuperscript{®} (tezacaftor/ivacaftor and ivacaftor) (n=1)**
    - The 1 discontinuation was due to constipation, which was considered unlikely related to study drug.
    - No deaths occurred in patients taking SYMDEKO.
    - There were no treatment discontinuations due to respiratory adverse events or transaminase elevations.
    - 4 patients had AEs that led to treatment interruption, none were considered serious, and all resolved without any treatment\textsuperscript{15,17}.
      - 2 were considered related or possibly related to study drug (blood creatine phosphokinase increased; ALT, AST, ALP, and GGT increased).

**Transaminase elevations\textsuperscript{12,15}\textsuperscript{a,b}**

<table>
<thead>
<tr>
<th>Elevated ALT or AST</th>
<th>SYMDEKO (N=70) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 x ULN</td>
<td>7 (10.0)\textsuperscript{a}</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>3 (4.5)\textsuperscript{a}</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

- 1 patient experienced liver enzyme elevations that led to study drug interruption\textsuperscript{15}.
- 4 patients experienced total bilirubin >1 to ≤1.5 x ULN\textsuperscript{17}.
- No patients experienced total bilirubin >1.5 x ULN\textsuperscript{15}.

\textsuperscript{a}Includes all patients who experienced transaminase elevations >3 x ULN, including those who experienced >5 and >8 x ULN\textsuperscript{17}.

\textsuperscript{b}Includes all patients who experienced transaminase elevations >5 x ULN, including those who experienced >8 x ULN\textsuperscript{15}.

### Incidence of adverse reactions in ≥10% of patients taking SYMDEKO

<table>
<thead>
<tr>
<th>Adverse Reactions (Preferred Term)</th>
<th>SYMDEKO (N=70) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>25 (35.7)</td>
</tr>
<tr>
<td>Infective pulmonary exacerbation of CF</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (10)</td>
</tr>
</tbody>
</table>

- 92.9% of patients (n=65) experienced at least 1 adverse event.

### Respiratory adverse events\textsuperscript{15}\textsuperscript{a}

- 2 patients (2.9%) experienced abnormal respiration (eg, chest tightness), which did not result in treatment discontinuation.

\textsuperscript{a}Serious adverse events included any adverse event that was fatal or life-threatening or resulted in hospitalization or prolonged hospitalization, disability/incapacity, congenital anomaly or birth defect, or an important medical event that required professional medical intervention.\textsuperscript{17}

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Reductions in sweat chloride were seen in the overall study population

**Trial 4 secondary endpoint**

-14.5 mmol/L DECREASE IN THE LS MEAN absolute change in sweat chloride from baseline through Week 24 (Baseline 99.1 mmol/L; 95% CI: -17.4, -11.6)

**IMPORTANT SAFETY INFORMATION**

**Concomitant Use With CYP3A Inducers**
- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort, is not recommended.

**Results for lung function, BMI, and CFQ-R**

**Trial 4 secondary endpoint (cont)**

Results for absolute and relative change in ppFEV₁

0.9 PERCENTAGE POINTS LS Mean absolute change in ppFEV₁ from baseline through Week 24 (Baseline 91.1%; 95% CI: -0.6, 2.3)

1.4 PERCENT LS Mean relative change in ppFEV₁ from baseline through Week 24 (Baseline 91.1%; 95% CI: -0.4, 3.1)

Results for BMI

+0.23 kg/m² LS MEAN ABSOLUTE CHANGE IN BMI from baseline at Week 24 (Baseline 17.44; 95% CI: 0.06, 0.40)

-0.03 LS MEAN ABSOLUTE CHANGE IN BMI-FOR-AGE Z-SCORE from baseline at Week 24 (Baseline 0.37; 95% CI: -0.10, 0.04)

Results for CFQ-R Respiratory Domain score (child version)

+3.4 POINT LS MEAN ABSOLUTE CHANGE in CFQ-R Respiratory Domain score from baseline through Week 24 (95% CI: 1.4, 5.5)

Patients age 6 through 11 years, homozygous for F508del or heterozygous for F508del and a mutation responsive to tezacaftor/ivacaftor.

CI, confidence interval; LS, least squares.
EVOLVE (TRIAL 1)

Patients with CF age 12 years and older who are homozygous for the F508del mutation in the CFTR gene

EVOLVE Study Design

Phase 3, 24-week, randomized, double-blind, placebo-controlled, two-arm study evaluating efficacy and safety of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)™

• Patients (N=504) were randomized to receive either tezacaftor/ivacaftor 100 mg/150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=248) or placebo q12h (n=256) with fat-containing food, in addition to their currently prescribed CF therapies

EVOLVE Study Population

• Selected inclusion criteria:— Confirmed CF diagnosis and clinically stable— Patients ≥12 years of age (mean age, 26.3 years) and homozygous for the F508del mutation— Percent predicted FEV1 (ppFEV1) ≥40% and ≤90% at screening (mean baseline ppFEV1, 60.0%)

• Selected exclusion criteria:
— History of colonization with organisms associated with a more rapid decline in pulmonary status, such as Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus
— Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN), or AST or ALT ≥5 x ULN

EVOLVE Endpoints

• Primary endpoint: Mean absolute change in ppFEV1, from baseline through Week 24 (please see page 16)™
• Key secondary endpoints: Relative change in ppFEV1 through Week 24, number of pulmonary exacerbations from baseline through Week 24 (please see pages 16, 18, and 19)™
• A hierarchical testing procedure was performed for primary and key secondary endpoints. For an endpoint to be significant, both it and all previous tests in the hierarchy had to achieve P ≤ 0.05™

EXTEND Interim Analysis

Interim analysis of the open-label extension study in patients who completed EVOLVE

See limitations and disclosures for the EXTEND Interim Analysis below

• Primary endpoint: To evaluate long-term safety and tolerability of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) (please see page 36)™
• Patients who completed EVOLVE were eligible to roll over into an ongoing, open-label, 96-week extension study™
— Results presented here are from an interim efficacy analysis of the extension study when approximately 70% of patients from EVOLVE had reached Week 24 of EXTEND™
— 91.2% of patients who completed EVOLVE rolled over into EXTEND™
— Those already receiving SYMDEKO continued taking it™
— Those previously taking placebo began taking SYMDEKO™
— The safety data were pooled across all cohorts and include all data available at the time of analysis™

EXTEND Interim Analysis Study Design

— Primary endpoint: Mean absolute change in ppFEV1, from baseline through Week 24 (please see page 16)™
— Key secondary endpoints: Relative change in ppFEV1 through Week 24, number of pulmonary exacerbations from baseline through Week 24, absolute change in BMI from baseline at Week 24, and absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score from baseline through Week 24 (please see pages 16, 18, and 19)™
— A hierarchical testing procedure was performed for primary and key secondary endpoints. For an endpoint to be significant, both it and all previous tests in the hierarchy had to achieve P≤0.05™

Limitations and Disclosures of EXTEND Open-Label Extension Study and Interim Analysis

• Enrollment in EXTEND was limited to only those patients who met strict inclusion criteria, completed specific Vertex studies investigating tezacaftor in combination with ivacaftor, and elected to enroll in EXTEND™
• The study was not a placebo-controlled study. All patients and investigators knew that subjects were on active drug, which may have introduced bias related to awareness of treatment™
• This was a planned interim analysis that analyzed efficacy data only for subjects who rolled over from EVOLVE, and analyses were conducted through the last visit at which approximately 70% of patients had completed, which was Week 24 in EXTEND™
• Results from EXTEND are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine whether within-arm changes were due to drug effect
• The safety data were pooled across all cohorts and include all data available at the time of analysis™
• Analyses are ongoing for the final data set, including other endpoints not presented herein™
— Data in the final analyses may differ from data reported in this interim analysis
• Due to limited total exposure at the time of the interim analysis, rare adverse events may not have been detected
• EXTEND may not meet the FDA definition of an adequate and well-controlled study due to its study design

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
EVOLVE (Trial 1): Improvements in lung function were seen in the overall population and pre-specified subgroups

**SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)—** Improvements in ppFEV₁ in EVOLVE persisted for up to an additional 24 weeks in an interim analysis

**Absolute Change in ppFEV₁ in EVOLVE**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2 (-3, -1)</td>
</tr>
<tr>
<td>D15</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>WK4</td>
<td>5 (4, 6)</td>
</tr>
<tr>
<td>WK8</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>WK12</td>
<td>-2 (-3, -1)</td>
</tr>
<tr>
<td>WK16</td>
<td>-3 (-4, -2)</td>
</tr>
<tr>
<td>WK24</td>
<td>-5 (-6, -4)</td>
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</tbody>
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**Absolute Change From Baseline in ppFEV₁ (percentage points), LS Mean (95% CI)**

<table>
<thead>
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**EXTEND Interim Analysis: Lung function (ppFEV₁) improvements in EVOLVE were maintained**

**Patients transitioning from placebo to SYMDEKO were rebaselined. Not all patients had completed Week 24 visit of the EXTEND Interim Analysis.**

**Results from the EXTEND Interim Analysis are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine statistical significance or whether within-arm changes were due to drug effect. Please see additional Limitations and Disclosures on page 15.**

**Cataracts**

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**Pediatric Use**

- The safety and efficacy of SYMDEKO in patients with CF younger than 6 years of age have not been studied.

Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.
Reduced rate of pulmonary exacerbations in EVOLVE persisted for up to an additional 24 weeks in an interim analysis

In EVOLVE: 5.1-point increase vs placebo in absolute change from baseline through Week 24 (95% CI: 3.2, 7.0) (not statistically significant due to testing hierarchy)\(^{12,18}\)

In EXTEND: mean change from baseline in CFQ-R Respiratory Domain score up to 48 weeks total SYMDEKO treatment was +3.1 points in patients continuing SYMDEKO. Patients transitioning to SYMDEKO had a change from baseline up to 24 weeks of +3.3 points\(^{20}\)

CFQ-R Respiratory Domain score evaluated respiratory symptoms including cough, sputum production, and difficulty breathing\(^{22}\)

Results from the EXTEND Interim Analysis are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine statistical significance or whether within-arm changes were due to drug effect. Please see additional Limitations and Disclosures on page 15.

Pulmonary exacerbations: Additional analyses
- 47% reduction in rate of pulmonary exacerbations requiring treatment with IV antibiotics vs placebo (RR: 0.53, 95% CI: 0.34, 0.82), not statistically significant\(^{20}\)
- The rate ratio for risk of pulmonary exacerbations requiring hospitalizations vs placebo was 0.78 (95% CI: 0.44, 1.36), not statistically significant\(^{20}\)

EVOLVE & EXTEND Interim Analysis: Results for BMI with SYMDEKO\(^\circledast\) (tezacaftor/ivacaftor and ivacaftor)\(^{12,18,20}\)

In EVOLVE at Week 24:
+0.06 kg/m\(^2\) within group change from baseline in patients continuing on SYMDEKO\(^{12,18}\)

In the EXTEND Interim Analysis up to an additional 24 weeks:
+0.26 kg/m\(^2\) within group change from baseline in patients transitioning from placebo to SYMDEKO\(^{21}\)

Results from the EXTEND Interim Analysis are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine statistical significance or whether within-arm changes were due to drug effect. Please see additional Limitations and Disclosures on page 15.

EVOLVE & EXTEND Interim Analysis: Results for CFQ-R Respiratory Domain score

- In EVOLVE: 5.1-point increase vs placebo in absolute change from baseline through Week 24 (95% CI: 3.2, 7.0) (not statistically significant due to testing hierarchy)\(^{12,18}\)
- In EXTEND: mean change from baseline in CFQ-R Respiratory Domain score up to 48 weeks total SYMDEKO treatment was +3.1 points in patients continuing SYMDEKO. Patients transitioning to SYMDEKO had a change from baseline up to 24 weeks of +3.3 points\(^{20}\)
- CFQ-R Respiratory Domain score evaluated respiratory symptoms including cough, sputum production, and difficulty breathing\(^{20}\)

Results from the EXTEND Interim Analysis are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine statistical significance or whether within-arm changes were due to drug effect. Please see additional Limitations and Disclosures on page 15.

Patients continuing on SYMDEKO had an estimated annual rate of 0.72 events/year\(^{20}\)
Those transitioning to SYMDEKO from placebo had an estimated annual rate of 0.58 events/year\(^{20}\)

Results from the EXTEND Interim Analysis are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine statistical significance or whether within-arm changes were due to drug effect. Please see additional Limitations and Disclosures on page 15.

Serious Adverse Reactions
- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs. 0 placebo patients

RR, relative risk.
*Estimated event rate per year calculated using 48 weeks per year.\(^{18}\)

IMPORTANT SAFETY INFORMATION

Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.\(^{15}\)
### ENCourAGE (TRIAL 661-114)

**Patients with CF age 12 years and older who are homozygous for F508del mutation and who previously discontinued lumacaftor/ivacaftor due to respiratory adverse events**

#### Study Design
- Phase 3b, 8-week, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)
  - Patients (N=97) received tezacaftor/ivacaftor (100 mg/150 mg qd) and ivacaftor (150 mg qd) 12 hours apart (n=50) or placebo q12h (n=47)
  - Treatment was taken with fat-containing food
  - Patients continued to take their prescribed CF therapies

#### Study Population
- Selected inclusion criteria
  - Confirmed CF diagnosis and clinically stable
  - Patients aged ≥12 years of age (mean age, 34.3 years for SYMDEKO and 33.3 for placebo) and homozygous for the F508del mutation
  - Percent predicted FEV1 (ppFEV1) ≥25 and ≤90 at screening (mean baseline ppFEV1, 44.6 for SYMDEKO and 48.0 for placebo)
  - Prior discontinuation of lumacaftor/ivacaftor due to respiratory adverse events*, with at least 1 respiratory sign or symptom considered related to treatment, including asymptomatic reduction in relative change in ppFEV1, >12% within 2 weeks after starting lumacaftor/ivacaftor
  - Discontinuation of lumacaftor/ivacaftor must have occurred within approximately 12 weeks from the most recent initiation of lumacaftor/ivacaftor, and events had to resolve or stabilize ≥28 days prior to screening
- Selected exclusion criteria
  - History of colonization with organisms associated with a more rapid decline in pulmonary status such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*
  - Two or more abnormal liver function tests at screening (ALT, AST, ALP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN), or ALT or AST ≥5 x ULN
  - Hepatic impairment (Child-Pugh Class B or C)
  - History of lung transplantation since most recent initiation of lumacaftor/ivacaftor
  - Acute upper or lower respiratory infection, pulmonary exacerbation, or change in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug)

---

*Respiratory adverse events of special interest (RAESI) included chest discomfort, dyspnea (shortness of breath), respiration abnormal (chest tightness), asthma, bronchial hyperreactivity, bronchospasm, and wheezing.*

---

**Endpoints**
- **Primary endpoint**
  - Incidence of respiratory adverse events of special interest (please see page 22)*
- **Key secondary endpoint**
  - Absolute change in ppFEV1, from baseline to the average of the Day 28 and Day 56 measurements (please see page 25)
- **Secondary endpoints**
  - Relative change in ppFEV1, from baseline to the average of the Day 28 and Day 56 measurements (please see page 25)
  - Absolute change in CFQ-R Respiratory Domain score from baseline to the average of the Day 28 and Day 56 measurements (please see page 25)
  - Tolerability based on study drug discontinuation through Day 56
  - Safety assessments based on adverse events, clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis), vital signs, pulse oximetry, and post-dose spirometry (please see pages 22, 23, and 24)

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

*Respiratory adverse events of special interest (RAESI) included chest discomfort, dyspnea (shortness of breath), respiration abnormal (chest tightness), asthma, bronchial hyperreactivity, bronchospasm, and wheezing.*
Trial 661-114: Incidence of respiratory adverse events and safety results

Primary endpoint: Incidence of respiratory adverse events

**OVERALL RATES OF RESPIRATORY ADVERSE EVENTS OF SPECIAL INTEREST**

14.0% of patients treated with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and 9 patients (19.1%) on placebo

21.3% of patients treated with placebo (n=10)

Analysis of respiratory adverse events assessed in Trial 661-114

<table>
<thead>
<tr>
<th>Respiratory Events</th>
<th>SYMDEKO (N=50) Patients with events, n (%)</th>
<th>Placebo (N=47) Patients with events, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>5 (10.0)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Respiration abnormal</td>
<td>3 (6.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>0</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No patients had respiratory adverse events that were classified as serious or led to treatment discontinuation

Discontinuations

- The proportion of patients who discontinued study drug due to adverse events was:
  - 4.0% of patients treated with SYMDEKO®
  - 2.1% of patients treated with placebo

- 1 death occurred in a patient taking SYMDEKO due to sepsis and multiple organ dysfunction following influenza infection, which was not considered to be related to study drug by the investigator

Transaminase elevations

- No patients experienced ALT or AST elevations >3 x ULN in Trial 661-114
  - Note: Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. See page 5 for Important Safety Information

Trial 661-114: Safety results (cont)

Serious adverse events

- Serious adverse events occurred in 5 patients (10.0%) on SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and 9 patients (19.1%) on placebo
- Serious adverse events, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included constipation, 1 (2.0%); multiple organ dysfunction syndrome, 1 (2.0%); sepsis, 1 (2.0%); and suicidal ideation, 1 (2.0%).

Most common adverse events

- Adverse events occurred in 37 patients (74.0%) on SYMDEKO and 39 patients (83.0%) on placebo

Incidence of adverse events occurring at a rate of ≥3% of patients taking SYMDEKO and greater than placebo

<table>
<thead>
<tr>
<th>Events</th>
<th>SYMDEKO (N=50) Patients with events, n (%)</th>
<th>Placebo (N=47) Patients with events, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>9 (18.0)</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (12.0)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Bacterial test positive</td>
<td>3 (6.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3 (6.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Respiration abnormal</td>
<td>3 (6.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>2 (4.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Increased viscosity of bronchial secretion</td>
<td>2 (4.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>2 (4.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>2 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>Productive cough</td>
<td>2 (4.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (4.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>2 (4.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Trial 661-114: Safety results (cont)

**Post-dose spirometry assessments**

<table>
<thead>
<tr>
<th>Time point</th>
<th>SYMDEKO mean (SD)</th>
<th>Placebo mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dose</td>
<td>45.1 (16.2)</td>
<td>48.0 (18.1)</td>
</tr>
<tr>
<td>n=48</td>
<td>n=47</td>
<td></td>
</tr>
<tr>
<td>2 hours post-dose</td>
<td>-0.6 (2.1)</td>
<td>0.3 (1.9)</td>
</tr>
<tr>
<td>n=45</td>
<td>n=43</td>
<td></td>
</tr>
<tr>
<td>4 hours post-dose</td>
<td>-0.8 (4.3)</td>
<td>0.0 (1.9)</td>
</tr>
<tr>
<td>n=45</td>
<td>n=43</td>
<td></td>
</tr>
</tbody>
</table>

The analysis included all patients who had a non-missing assessment at the pre-dose time point and at least 1 non-missing post-dose assessment.26

- During initiation of treatment, 1 patient (2.2%) on SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) experienced a ≥20% absolute decline in ppFEV₁, 4 hours post-dose on Day 1.25

**IMPORTANT SAFETY INFORMATION**

**Most Common Adverse Reactions**
- The most common adverse reactions in Trials 1 and 3 occurring in ≥3% of patients treated with SYMDEKO (N=334) and at a higher rate than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness.
- The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3.

**Transaminase (ALT or AST) Elevations**
- Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered.
- Dosing should be interrupted in patients with significant elevations of transaminases (e.g., ALT or AST >5x upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN) and laboratory tests should be closely followed until abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment.

**Results for absolute and relative change in ppFEV₁**

**Key Secondary Endpoint**
- 2.7 Percentage Points Treatment Difference vs Placebo in absolute change in ppFEV₁, from baseline to the average of the Day 28 and Day 56 measurements (95% CI: 0.1, 4.4)

**Secondary Endpoint**
- 6.7 Percent Treatment Difference vs Placebo in relative change in ppFEV₁ from baseline to the average of the Day 28 and Day 56 measurements (95% CI: 2.5, 10.9)

**Results for CFQ-R Respiratory Domain score**

**Secondary Endpoint**
- 1.1 Point Mean Treatment Difference vs Placebo in absolute change in CFQ-R Respiratory Domain score from baseline to the average of the Day 28 and Day 56 measurements (95% CI: -4.9, 7.0)

- The mean score was 5.7 points for SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and 4.7 points for placebo.

The MCID threshold for CFQ-R Respiratory Domain scores is 4 points in patients with CF with stable respiratory symptoms, which is the minimal change a patient can detect.17

Hypothesis testing was not planned or performed to compare SYMDEKO and placebo for efficacy results in this trial; therefore, statistical significance cannot be determined.

Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.
EXPAND (TRIAL 2) Patients age 12 years and older with CF heterozygous for F508del and a mutation predicted to be responsive to tezacaftor/ivacaftor

**Study Design**

EXPAND was a 2-period, 3-treatment, 8-week crossover study. There were two 8-week dosing periods separated by an 8-week washout.

- **Patients** (N=244) were randomized to receive one treatment sequence taken with fat-containing food, in addition to their currently prescribed CF therapies: tezacaftor/ivacaftor 100 mg/150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=161), ivacaftor 150 mg alone (n=156), or placebo q2h (n=161); patients received 2 of 3 treatment options.

**Study Population**

- **Selected inclusion criteria**
  - Confirmed CF diagnosis and clinically stable
  - Patients ≥12 years of age (mean age 34.8 years)
  - Patients with splice mutations. 93 received SYMDEKO and 97 received placebo. Of patients with missense mutations, 66 received SYMDEKO and 63 received placebo.
  - Percent predicted FEV1 (ppFEV1) ≥40% and ≤60% at screening (mean baseline FEV1, 62.3%).
  - History of colonization with organisms associated with a more rapid decline in pulmonary status, such as Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus.
  - Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥2 x ULN or total bilirubin ≥2 x ULN).

**Endpoints**

- **Primary endpoint:** Mean absolute change in ppFEV1 from baseline to the average of Week 4 and Week 8 (please see page 30).
- **Selected key secondary endpoint:** Absolute change in CFQ-R Respiratory Domain score from baseline to the average of Week 4 and Week 8 (please see page 30).

Additional mutations determined to be responsive to tezacaftor/ivacaftor based on in vitro data and were not studied in EXPAND or any other clinical setting were: A1067T, D104E, D1070N, E193K, E56K, F1052V, F1074L, K1060T, R174A, R174W.

**Interim Analysis**

Interim analysis of the open-label extension study in patients who completed EXPAND

**Study Design**

- Enrolment in EXTEND was limited to only those patients who met strict inclusion criteria, completed specific Vertex studies investigating tezacaftor in combination with ivacaftor, and elected to enroll in EXTEND.
- The study was not a placebo-controlled study. All patients and investigators knew that subjects were on active drug, which may have introduced bias related to awareness of treatment.
- Due to limited total exposure at the time of the interim analysis, rare adverse events may not have been detected.
- EXTEND may not meet the FDA definition of an adequate and well-controlled study.
- Enrollment in EXTEND was limited to those patients who met strict inclusion criteria, completed specific Vertex studies investigating tezacaftor in combination with ivacaftor, and elected to enroll in EXTEND.
- The study was not a placebo-controlled study. All patients and investigators knew that subjects were on active drug, which may have introduced bias related to awareness of treatment.
- RESULTS: The study was not a placebo-controlled study. All patients and investigators knew that subjects were on active drug, which may have introduced bias related to awareness of treatment.
- Due to limited total exposure at the time of the interim analysis, rare adverse events may not have been detected.
- EXTEND may not meet the FDA definition of an adequate and well-controlled study due to its study design.

See limitations and disclosures for the EXTEND Interim Analysis below

- **Primary endpoint:** To evaluate long-term safety and tolerability of SYMDEKO (tezacaftor/ivacaftor and ivacaftor) (please see page 36).
- Those already receiving SYMDEKO continued taking it.
- Those previously in another treatment arm began taking SYMDEKO.
- The safety data were pooled across all cohorts and include all data available at the time of analysis.

**Limitations and Disclosures of EXTEND Open-Label Extension Study and Interim Analysis**

- Enrolment in EXTEND was limited to only those patients who met strict inclusion criteria, completed specific Vertex studies investigating tezacaftor in combination with ivacaftor, and elected to enroll in EXTEND.
- The study was not a placebo-controlled study. All patients and investigators knew that subjects were on active drug, which may have introduced bias related to awareness of treatment.
- This was a planned interim analysis that analyzed efficacy data only for subjects who rolled over from EXPAND, and analyses were conducted through the last visit at which approximately 70% of patients had completed, which was Week 16 in EXTEND.
- Results from EXTEND are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine whether within-arm changes were due to drug effect.
- The safety data were pooled across all cohorts and include all data available at the time of analysis.
- Analyses are ongoing for the final data set, including other endpoints not presented herein.
- Data in the final analyses may differ from data reported in this interim analysis.
- Due to limited total exposure at the time of the interim analysis, rare adverse events may not have been detected.
- EXTEND may not meet the FDA definition of an adequate and well-controlled study due to its study design.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Adding tezacaftor to ivacaftor led to improvement in lung function

**EXPAND (Trial 2):** Significant improvement by Day 15 in lung function with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) through 8 weeks.26

**EXTEND Interim Analysis:** Lung function improvements in ppFEV1 in EXPAND were maintained.20

**SIGNIFICANT IMPROVEMENT IN PRIMARY ENDPOINT**

- **PERCENTAGE POINTS IMPROVEMENT VS PLACEBO** in mean absolute change in ppFEV1 from baseline to the average of Weeks 4 and 8 (95% CI: 5.7, 7.8; P=0.0001).12

- Improvements in ppFEV1, compared to placebo in patients with splice and missense mutations were 7.4 percentage points (95% CI: 6.0, 8.7) and 5.9 percentage points (95% CI: 4.2, 7.5), respectively.21

- For individual mutations, changes in ppFEV1, varied by genotype and ranged from -1.0 to 10.1; see full Prescribing Information for results by mutation. These were ad hoc analyses.12,24

**SIGNIFICANT IMPROVEMENT IN OTHER EFFICACY ANALYSIS**

- **PERCENTAGE POINTS IMPROVEMENT VS IVACAFTOR** in mean absolute change in ppFEV1 from baseline to the average of Weeks 4 and 8 (95% CI: 1.2, 2.9; P<0.0001).12

- Improvements were seen in mean absolute change in ppFEV1 vs placebo across pre-specified subgroups.12,25

- Regardless of age, baseline ppFEV1, sex, mutation class, colonization with Pseudomonas, concomitant use of standard-of-care medications for CF, and geographic region

**Changes in ppFEV1, from baseline vs placebo to the average of Weeks 4 and 8**12,25,26

**IMPORTANT SAFETY INFORMATION**

- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort, is not recommended.

**Concomitant Use With CYP3A Inducers**

- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort, is not recommended.

Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.
Results for CFQ-R Respiratory Domain Score in EXPAND

**EXPAND (Trial 2): Absolute change from baseline in CFQ-R Respiratory Domain score with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**

**SIGNIFICANT IMPROVEMENT VS PLACEBO**

<table>
<thead>
<tr>
<th>11.1 POINT IMPROVEMENT</th>
<th>1.4 POINT TREATMENT DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>from baseline to the average of Weeks 4 and 8 (95% CI: 8.7, 13.6; P&lt;0.0001)</td>
<td>from baseline to the average of Weeks 4 and 8 (95% CI: -1.0, 3.9; not statistically significant)</td>
</tr>
</tbody>
</table>

- The CFQ-R Respiratory Domain score evaluated respiratory symptoms including cough, sputum production, and difficulty breathing.

**CFQ-R: Ad hoc Analyses**

- Improvements in CFQ-R Respiratory Domain score compared to placebo in patients with splice and missense mutations were 9.5 points (95% CI: 6.3, 12.7) and 13.4 points (95% CI: 9.6, 17.3), respectively.
- For individual mutations, changes in CFQ-R Respiratory Domain score varied by genotype and ranged from -11.1 to 29.2; see full Prescribing Information for results by mutation.

The MCID threshold for CFQ-R Respiratory Domain scores is 4 points in patients with CF with stable respiratory symptoms, which is the minimal change a patient can detect.

**IMPORTANT SAFETY INFORMATION**

- **Cataracts**
  - Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO.
- **Pediatric Use**
  - The safety and efficacy of SYMDEKO in patients with CF younger than 6 years of age have not been studied.

Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.
SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) safety profile demonstrated in clinical trials

Safety data from 3 placebo-controlled clinical trials

- The overall safety profile is based on data from three double-blind, placebo-controlled Phase 3 clinical trials: 2 parallel-group trials of 12- and 24-week duration and one cross-over design trial of 8-week duration. Eligible patients were also able to participate in an open-label extension safety study (up to 96 additional weeks of SYMDEKO).
- In the three placebo-controlled Phase 3 trials, a total of 496 patients with CF aged 12 years and older received at least one dose of SYMDEKO.
- The proportion of patients who discontinued study drug prematurely due to adverse events was:
  
<table>
<thead>
<tr>
<th></th>
<th>SYMDEKO Treated</th>
<th>Placebo Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6% of patients</td>
<td>2.0% of patients</td>
<td></td>
</tr>
</tbody>
</table>

Laboratory abnormalities: Transaminase elevations

- The safety profile of SYMDEKO was generally similar across all subgroups of patients, including analysis by age, sex, baseline ppFEV₁, and geographic regions.
- There were no deaths in the placebo-controlled studies, and one death in the open-label extension study due to respiratory failure and influenza infection in a patient who had discontinued SYMDEKO 7 weeks prior, which was not considered to be related to the study drug by the investigator.
- The incidence of transaminase elevations was similar between treatment groups:
  - One patient (0.2%) on SYMDEKO and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases.
  - No patients treated with SYMDEKO experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN.

Incidence of maximum transaminases during placebo-controlled trials

<table>
<thead>
<tr>
<th>Elevated ALT or AST</th>
<th>SYMDEKO %</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 X ULN</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>&gt;5 X ULN</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;8 X ULN</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) safety profile demonstrated in clinical trials (cont)

Cataracts

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO.

Serious adverse reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) SYMDEKO-treated patients vs. 0 placebo patients.

Most common adverse reactions

- The safety profile for patients with CF enrolled in EXPAND (Trial 2) was similar to that observed in EVOLVE and Trial 3.

Incidence of adverse reactions in ≥3% of patients taking SYMDEKO and greater than placebo (EVOLVE [Trial 1] and Trial 3)

<table>
<thead>
<tr>
<th>Adverse Reactions (Preferred Term)</th>
<th>SYMDEKO (N=334) n (%)</th>
<th>Placebo (N=343) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>49 (15)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (9)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>13 (4)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (4)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

- The safety profile for patients with CF enrolled in EXPAND (Trial 2) was similar to that observed in EVOLVE and Trial 3.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Pooled analysis of respiratory adverse events in clinical trials of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

Rates of respiratory adverse events

11.3% OF PATIENTS TREATED WITH SYMDEKO (N=56)

14.7% OF PATIENTS TREATED WITH PLACEBO (N=74)

• The median time to onset for any respiratory adverse event was 59 days with SYMDEKO vs 38 days with placebo.

Results of post-dose spirometry assessments in patients age 12 to <18 years

• During initiation of treatment with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), spirometry showed no evidence of an acute drop (defined as a decrease in ppFEV₁ of ≥10 percentage points) in a subset of patients age 12 to <18 years.

Absolute change in ppFEV₁, from pre-dose to post-dose in patients aged 12 to <18 years at screening

The analysis included all subjects age 12 to 18 years who had a non-missing assessment at the pre-dose time point and at least 1 non-missing post-dose assessment. The sample size for this assessment was limited by the number of subjects who completed the Day 1 and Day 15 visits. Data were pooled from EVOLVE, EXPAND, and Trial 3. Due to the crossover design of EXPAND, patients may have received 2 periods of treatment, and therefore, may have results for both SYMDEKO and placebo.

Pooled analysis of respiratory adverse events in clinical trials of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) (cont)

Pooled analysis of respiratory events

Respiratory Events

<table>
<thead>
<tr>
<th>SYMDEKO (N=496)</th>
<th>Placebo (N=505)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>Patients with events, n (%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>30 (6.0)</td>
</tr>
<tr>
<td>Respiration abnormal</td>
<td>15 (3.0)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Asthma</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>0</td>
</tr>
</tbody>
</table>

Respiratory event rates by baseline ppFEV₁ subgroups

<table>
<thead>
<tr>
<th>Baseline ppFEV₁</th>
<th>SYMDEKO % (n/N)</th>
<th>Placebo % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40 (SYMDEKO range: 30.3 to &lt;40; Placebo range: 27.8 to &lt;40)</td>
<td>14.3% (7/49)</td>
<td>27.9% (12/43)</td>
</tr>
<tr>
<td>240 to &lt;70 (SYMDEKO range: 70 to 96.7; Placebo range: 70 to 96.2)</td>
<td>12.5% (38/304)</td>
<td>16.8% (52/310)</td>
</tr>
<tr>
<td>≥70</td>
<td>7.7% (11/142)</td>
<td>6.6% (10/152)</td>
</tr>
</tbody>
</table>

Safety profile in a specific population: Patients with severe lung dysfunction (ppFEV₁, <40)

• EVOLVE and EXPAND included a total of 39 patients treated with SYMDEKO with ppFEV₁ <40 at baseline (range 30 to 40)
  — In EVOLVE, 23 patients treated with SYMDEKO and 24 placebo-treated patients had ppFEV₁ <40
  — In EXPAND, 16 patients treated with SYMDEKO, 15 placebo-treated, and 13 ivacaftor-treated patients had ppFEV₁ <40
• The safety profile in this subgroup was comparable to the overall results observed in both EVOLVE and EXPAND.

*Trial 3 was a two-arm study that compared SYMDEKO to placebo in patients with CF aged 12 years and older who were heterozygous for the F508del mutation and had a second CFTR mutation not responsive to SYMDEKO. This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.

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

*Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.
Safety results in the EXTEND Interim Analysis were consistent with pivotal trials

Safety results for SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) from the EXTEND Interim Analysis

- Results presented are from interim analyses. Data in additional interim analyses and the final analysis may differ from what is presented here
- Incidence of adverse events are expected to increase as the mean exposure to study drug increases

**867 PATIENTS RECEIVED ≥1 DOSE OF SYMDEKO**

- 33.5 WEEKS MEAN EXPOSURE

- 0.8% of patients had adverse events leading to treatment discontinuation
- Serious adverse events occurring in ≥1% of patients taking SYMDEKO were infective pulmonary exacerbation of CF (13.5%) and hemoptysis (1.8%)
- There was 1 death in the open-label extension study due to respiratory failure and influenza infection in a patient who had discontinued SYMDEKO 7 weeks prior

### Most common adverse events occurring in ≥10% of patients

<table>
<thead>
<tr>
<th>Events</th>
<th>Patients With Events n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any adverse event</td>
<td>713 (82.2)</td>
</tr>
<tr>
<td>Infective pulmonary exacerbation of CF</td>
<td>288 (33.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>194 (22.4)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>100 (11.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>97 (11.2)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>96 (11.3)</td>
</tr>
</tbody>
</table>

- The majority of adverse events were considered mild or moderate in severity
  - Patients with adverse events by maximum severity: mild (30.4%), moderate (41.3%), severe (10.0%), and life threatening (0.2%)
- 3.2% of patients experienced elevated transaminases, the majority of which were considered mild in severity

Additional safety information for SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) from EXTEND

- Results presented are from interim analyses. Data in additional interim analyses and the final analysis may differ from what is presented here
- Incidence of adverse events are expected to increase as the mean exposure to study drug increases

**613 PATIENTS RECEIVED ≥48 WEEKS OF SYMDEKO**

- 86.0 WEEKS MEAN EXPOSURE

- 0.5% of patients had adverse events leading to treatment discontinuation
- Serious adverse events occurring in ≥1% of patients taking SYMDEKO were infective pulmonary exacerbation of CF (21.5%), hemoptysis (3.4%), DIOS (11%), and pneumonia (1.0%)

### Most common adverse events occurring in ≥10% of patients

<table>
<thead>
<tr>
<th>Events</th>
<th>Patients With Events n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any adverse event</td>
<td>601 (98.0)</td>
</tr>
<tr>
<td>Infective pulmonary exacerbation of CF</td>
<td>331 (54.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>240 (39.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>156 (25.4)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>137 (22.3)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>122 (19.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>115 (18.8)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>97 (15.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>93 (15.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>77 (12.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>77 (12.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>72 (11.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>70 (11.4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>68 (11.1)</td>
</tr>
</tbody>
</table>

- The majority of adverse events were considered mild or moderate in severity
  - Patients with adverse events by maximum severity: mild (27.1%), moderate (52.9%), severe (17.6%), and life threatening (0.5%)
- 8.0% of patients experienced elevated transaminases, the majority of which were mild
  - There were 4 patients (0.7%) with elevated transaminases that were considered serious

DIOS, distal intestinal obstruction syndrome

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Potential drug interactions with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

Clinical considerations are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

Drugs shown within a therapeutic class do not represent all possible drugs within the class. Drugs within a class may have different metabolic profiles, and therefore, clinical recommendations apply only to the drugs named and not the class. The table does not represent all possible drugs or drug classes that a patient could be receiving.

### Reducer Blood Levels of SYMDEKO Expected with Strong CYP3A Inducers

The concomitant use of CYP3A inducers may reduce tezacaftor and ivacaftor blood levels, potentially resulting in reduced SYMDEKO efficacy. Co-administration of strong CYP3A inhibitors is not recommended.

#### Examples of Strong CYP3A Inducers
- Rifampin
- Rifabutin
- Phenytoin
- St. John’s wort (Hypericum perforatum)

### Increased Blood Levels of SYMDEKO Expected with Strong or Moderate CYP3A Inhibitors

SYMDEKO dosing adjustment is recommended for co-administration with strong or moderate CYP3A inhibitors (see dose adjustments on following page).

#### Examples of Strong CYP3A Inhibitors
- Ketoconazole
- Itraconazole
- Posaconazole
- Fluconazole
- Erythromycin

#### Examples of Moderate CYP3A Inhibitors
- Voriconazole
- Telithromycin
- Clarithromycin
- Grapefruit
- Seville oranges

### Increased Exposure to These Drugs May Occur with SYMDEKO

Ivacaftor may inhibit CYP2C9 and increase exposures of these drugs.

#### Example of CYP2C9 Substrate
- Monitor international normalized ratio of: Warfarin

SYMDEKO increased digoxin exposure and may increase exposure of other sensitive P-gp substrates.

#### Examples of P-gp Substrates
- Digoxin
- Cyclosporine
- Everolimus
- Sirolimus
- Tacrolimus

### Drugs Not Expected to Have a Clinically Significant Effect on SYMDEKO or Vice Versa

- Oral contraceptives (estrogen/progestins)
- Specific antidepressants (desipramine, citalopram, escitalopram, sertraline, mirtazapine, paroxetine, trazodone)
- Azithromycin
- CYP3A substrates (e.g., midazolam [oral])
- Ciprofloxacin

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

### Dosing and Administration

A regimen of a tezacaftor/ivacaftor tablet taken in the morning and an ivacaftor tablet taken in the evening, approximately 12 hours apart.

#### Recommended Dose

**Patients age 6 through 11 years, weighing <30 kg**

<table>
<thead>
<tr>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tezacaftor 60 mg</td>
<td>Ivacaftor 15 mg</td>
</tr>
</tbody>
</table>

**Patients age 12 years and older**

<table>
<thead>
<tr>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tezacaftor 100 mg</td>
<td>Ivacaftor 150 mg</td>
</tr>
</tbody>
</table>

### Recommended Dose Adjustments

#### Severe Hepatic Impairment (Child-Pugh Class C)

- Use with caution or use frequently
- Tezacaftor/ivacaftor dose
- No ivacaftor dose

#### Moderate Hepatic Impairment (Child-Pugh Class B)

- Tezacaftor/ivacaftor dose
- No ivacaftor dose

### Dosing for Concomitant Use with CYP3A Inducers or Inhibitors

- No dose adjustments are necessary for mild hepatic impairment.
- Studies have not been conducted in patients with severe hepatic impairment.
- Use with caution at an adjusted dose after weighing the risks and benefits of treatment.
- No dose adjustment necessary for mild/moderate CYP3A inducers or mild CYP3A inhibitors.
- Continue to alternate tablets every day.

- SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) should always be taken with fat-containing food to ensure adequate absorption. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats.
- Patients should continue taking their other CF therapies as prescribed.
- SYMDEKO has not been studied in patients with moderate or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is recommended for mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment or end-stage renal disease.
- The safety and efficacy of SYMDEKO in patients with CF younger than 6 years of age have not been studied.

*Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (AUC) by 89%. Tezacaftor exposures can also be expected to decrease significantly.*

*Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure (AUC) by 4.0-fold and ivacaftor by 15.6-fold.*

*Co-administration with fluconazole, a moderate CYP3A inhibitor, increased ivacaftor exposure (AUC) by 3.0-fold and may increase tezacaftor exposure by approximately 2.0-fold.*

*AUC, area under the curve; DDI, drug-drug interaction.*
Missed Dose
IF 66 HOURS have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule.

NEXT SCHEDULED DOSE can be taken at the usual time. More than one dose should not be taken at the same time.

Packaging
- SYMDEKO is supplied in cartons containing 4 weekly blister cards, each with 14 tablets.
- Each SYMDEKO carton consists of a tezacaftor/ivacaftor fixed-dose combination tablet and an ivacaftor tablet.

Packaging for Patients Age 6 Through 11 Years Weighing <30 kg
- The tezacaftor/ivacaftor fixed-dose combination tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 50 mg of tezacaftor and 75 mg of ivacaftor.
- Ivacaftor tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 75 mg of ivacaftor.

Packaging for Patients Age 12 Through 11 Years Weighing ≥30 kg
- The tezacaftor/ivacaftor fixed-dose combination tablets are supplied as yellow, capsule-shaped tablets containing 150 mg of tezacaftor and 150 mg of ivacaftor.
- Ivacaftor tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor.

References:
FOR PATIENTS WITH CF AGE 6 YEARS AND OLDER WHO ARE HOMOZYGOUS FOR THE F508DEL MUTATION OR HAVE A MUTATION PREDICTED TO BE RESPONSIVE TO SYMDEKO

**EVOLVE (Trial 1)**

Patients homozygous for the F508del mutation

**EXPAND (Trial 2)**

Patients heterozygous for F508del with a mutation predicted to be responsive to tezacaftor/ivacaftor

**SIGNIFICANT IMPROVEMENTS IN LUNG FUNCTION**

4.0 PERCENTAGE POINTS IMPROVEMENT VS PLACEBO in mean absolute change in ppFEV₁ from baseline through Week 24 (P<0.0001)

6.8 PERCENTAGE POINTS IMPROVEMENT VS PLACEBO in mean absolute change in ppFEV₁ from baseline to the average of Weeks 4 and 8 (P<0.0001)

**Safety Results**

- The proportion of patients who discontinued study drug prematurely due to adverse events was 1.6% of patients treated with SYMDEKO and 2.0% of patients treated with placebo.
- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs. 0 placebo patients.
- The most common adverse reactions in patients treated with SYMDEKO (Trials 1 and 3) with an incidence of ≥3% and at a higher incidence for patients treated with SYMDEKO (N=334) than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness.
- During the placebo-controlled Phase 3 trials (up to 24 weeks), the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x upper limit of normal were similar between patients treated with SYMDEKO and placebo-treated patients; 0.2%, 1.0%, and 3.4% in patients treated with SYMDEKO, and 0.4%, 1.0%, and 3.4% in placebo-treated patients.
- See pages 32-33 for additional safety profile information.

**ENCOURAGE (Trial 661-114)**

Patients homozygous for the F508del mutation who discontinued lumacaftor/ivacaftor due to respiratory adverse events

**RESPIRATORY ADVERSE EVENTS**

14.0% OF PATIENTS TREATED WITH SYMDEKO (n=7)

21.3% OF PATIENTS TREATED WITH PLACEBO (n=10)

- No patients had respiratory adverse events that were classified as serious or led to treatment discontinuation.
- 4.0% of patients treated with SYMDEKO discontinued study drug due to adverse events.

**TRIAL 4**

Patients homozygous or heterozygous for the F508del mutation or have a mutation predicted to be responsive to SYMDEKO

**SAFETY PROFILE WAS SIMILAR TO THAT OBSERVED IN PATIENTS AGE 12 YEARS AND OLDER**

*Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3. Trial 3 was a two-arm study that compared SYMDEKO to placebo in patients with CF aged 12 years and older who were heterozygous for the F508del mutation and had a second CFTR mutation not responsive to SYMDEKO. This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.*

Please click for Important Safety Information and full Prescribing Information for SYMDEKO. For more information, visit SYMDEKOhcp.com.