INDICATIONS AND USAGE
SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 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.
CF is a genetic, systemic disease that results in progressive lung disease and can ultimately lead to pulmonary failure.1,2

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

Estimated Decline in Lung Function in Patients With CF With Certain Genotypes From 2006 to 2014 Based on Analysis of the CFFPR1,4

- Mutations associated with residual CFTR activity
- FS508del homozygous

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Years From Baseline</th>
<th>Residual CFTR Activity (n)</th>
<th>FS508del (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-17</td>
<td>0 1 2</td>
<td>131</td>
<td>2195</td>
</tr>
<tr>
<td>18-24</td>
<td>0 1 2</td>
<td>165</td>
<td>2628</td>
</tr>
<tr>
<td>≥25</td>
<td>0 1 2</td>
<td>400</td>
<td>2849</td>
</tr>
</tbody>
</table>

Slope = -0.57a

Slope = -1.85

Slope = -2.37

Slope = -2.52

Slope = -1.06a

Slope = -1.86

Slope = -2.37

Slope = -1.85

Slope = -2.52

Slope = -1.06a

Slope = -1.86

Slope = -0.57a

Slope = -1.85

Slope = -2.37

Slope = -2.52

Slope = -1.06a

Slope = -1.86

Study overview: Retrospective analysis of patients in the US CF Foundation Patient Registry from 2006 to 2014. Objective was to characterize and compare rate of decline in patients homozygous for FS508del with patients heterozygous for FS508del 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 FS508del and may not be applicable to other genotypes.

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

- In patients with CF, 52% of FEV1 decline is associated with pulmonary exacerbations.1a
- By age 12, ~30% of patients will experience ≥1 pulmonary exacerbations per year.2
- Pulmonary exacerbations may have devastating effects on patients, including being associated with subsequent reductions in pulmonary function, which may be permanent.6,7

Structural lung damage may occur before spirometry detects loss of lung function.8,9

Even patients with CF who have normal percent predicted FEV1 (ppFEV1) may have evidence of structural lung damage.8,10

HRCT scan below shows evidence of pulmonary abnormalities in a 13-year-old patient with ppFEV1 of 96%.10

FEV1, forced expiratory volume in 1 second; HRCT, high-resolution computed tomography; PFT, pulmonary function test.


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


Study overview: Retrospective analysis of patients in the US CF Foundation Patient Registry from 2006 to 2014. Objective was to characterize and compare rate of decline in patients homozygous for FS508del with patients heterozygous for FS508del 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 FS508del and may not be applicable to other genotypes.

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• By age 12, ~30% of patients will experience ≥1 pulmonary exacerbations per year.2
• Pulmonary exacerbations may have devastating effects on patients, including being associated with subsequent reductions in pulmonary function, which may be permanent.6,7

*Case scenario of patient from study of 48 patients studied at Sophia Children’s Hospital in the Netherlands who received annual PFT and biennial HRCT scans. The mean age at the second HRCT was 13.04 years and the mean ppFEV1 was 76.0%. All PFT scans were done within 1 month of HRCT scanning and HRCT scans were performed as part of routine check-ups and thus patients were relatively stable. Image shows a patient at age 13 with ppFEV1 of 96%; HRCT scores: Castile 22, Brody 17, Helbich 12, Santamaria 13, and Bhalla 12. These scores assess various structural changes consistent with lung disease.6

FEV1, forced expiratory volume in 1 second; HRCT, high-resolution computed tomography; PFT, pulmonary function test.
Please click for full Prescribing Information for SYMDEKO.
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.
- 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.

**IMPORTANT SAFETY INFORMATION**

For patients with CF age 12 years and older

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

**CFTR Mutations That Produce CFTR Protein Responsive to SYMDEKO**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>AIDAN, 13</th>
<th>BARBARA, 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del/F508del</td>
<td>FS08del/FS08del</td>
<td>FS08del/FS08del</td>
</tr>
</tbody>
</table>

* A patient must have 2 copies of the F508del mutation or at least one copy of a responsive mutation listed above in this table to be indicated.
### 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).11,14

- 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

- **Key inclusion criteria**11,14
  - 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)
- **Key exclusion criteria**11
  - 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 10)11
- **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 10, 12, and 13)11,14
- 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<0.0511,15

### EXTEND Interim Analysis

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

#### EXTEND Interim Analysis 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 22)*
- **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 EXTEND16
  - 91.2% of patients who completed EVOLVE rolled over into EXTEND16
  - Those already receiving SYMDEKO continued taking it16
  - Those previously taking placebo began taking SYMDEKO16
  - The safety data were pooled across all cohorts and include all data available at the time of analysis16

#### EXTEND INTERIM ANALYSIS: LIMITATIONS AND DISCLOSURES

- 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 EXTEND16
- 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 treatment16
- 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 EXTEND16
- Results from EXTEND are based on an uncontrolled, open-label study; therefore, hypothesis testing cannot determine whether within-arm changes were due to drug effect16
- The safety data were pooled across all cohorts and include all data available at the time of analysis16
- Analyses are ongoing for the final data set, including other endpoints not presented herein16
  - 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

#### AIDAN, 13

| F508del/F508del |

**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) showed improvements in mean absolute change in ppFEV₁ in EVOLVE.**

<table>
<thead>
<tr>
<th>Subgroups by baseline ppFEV₁</th>
<th>Absolute change in ppFEV₁, from baseline (percentage points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(SYMDEKO n=23, placebo n=24, range 27.8% to &lt;40%)</td>
<td>&lt;40% +3.5 (95% CI: 10, 6.1)</td>
</tr>
<tr>
<td>(SYMDEKO n=156, placebo n=152)</td>
<td>≥40 to &lt;70% +4.2 (95% CI: 31, 5.2)</td>
</tr>
<tr>
<td>(SYMDEKO n=66, placebo n=80, range ≥70% to 96.2%)</td>
<td>≥70% +3.7 (95% CI: 2.2, 5.2)</td>
</tr>
</tbody>
</table>

*Results are from an interim analysis when approximately 70% of patients from EVOLVE had reached Week 24 of EXTEND.*

**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 9.**

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

**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.

**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.
**Reduced rate of pulmonary exacerbations in EVOLVE persisted for up to an additional 24 weeks in an interim analysis**

**EVOLVE (Trial 1): SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) significantly reduced the rate of pulmonary exacerbations vs placebo**11,14

**Annualized Rate of Pulmonary Exacerbations Through Week 2411,14**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=256)</th>
<th>SYMDEKO (N=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.99 (95% CI: 0.72, 1.36)</td>
<td>0.64 (95% CI: 0.48, 0.88)</td>
</tr>
<tr>
<td>35% Reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Results for BMI and CFQ-R in EVOLVE and EXTEND Interim Analysis**

**EVOLVE & EXTEND Interim Analysis: Results for BMI with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**11,14,16

- **In EVOLVE at Week 24**:
  - +0.06 kg/m² in the SYMDEKO group vs placebo (95% CI: -0.08, 0.19) (not statistically significant)

- **In the EXTEND Interim Analysis up to an additional 24 weeks**:
  - +0.26 kg/m² within group change from baseline in patients continuing on SYMDEKO16

**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)11,14,16
- **In the EXTEND Interim Analysis**:
  - 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 points16
  - CFQ-R Respiratory Domain score evaluated respiratory symptoms including cough, sputum production, and difficulty breathing18

**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 9.**

**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 significant11,14
- The rate ratio for risk of pulmonary exacerbations requiring hospitalizations vs placebo was 0.78 (95% CI: 0.44, 1.36), not statistically significant11,14

**EXTEND Interim Analysis: Lower rate of pulmonary exacerbations in EVOLVE was maintained for up to an additional 24 weeks**

- Patients continuing on SYMDEKO had an estimated annual rate of 0.72 events/year16
- Those transitioning to SYMDEKO from placebo had an estimated annual rate of 0.58 events/year16

**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 9.**

**Pediatric Use**

- The safety and efficacy of SYMDEKO in patients with CF younger than 12 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%) SYMDEKO-treated patients vs. 0 placebo patients

Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.
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)\(^{20}\)
- 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)\(^{20,21}\)
  - Treatment was taken with fat-containing food
  - Patients continued to take their prescribed CF therapies

Study Population
- Key inclusion criteria\(^{20,21}\)
  - 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
- Key exclusion criteria\(^{21}\)
  - 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)

Endpoints
- Primary endpoint\(^{20}\)
  - Incidence of respiratory adverse events of special interest\(^{*}\)
- Key secondary endpoint\(^{20}\)
  - Absolute change in ppFEV1, from baseline to the average of the Day 28 and Day 56 measurements
- Secondary endpoint\(^{20,21}\)
  - Relative change in ppFEV1, from baseline to the average of the Day 28 and Day 56 measurements
  - Absolute change in CFQ-R Respiratory Domain score from baseline to the average of the Day 28 and Day 56 measurements
  - 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

*Respiratory adverse events of special interest (RAESI) included chest discomfort, dyspnea (shortness of breath), respiration abnormal (chest tightness), asthma, bronchial hyperreactivity, bronchospasms, and wheezing.\(^{20}\)

Limitations and Disclosures of ENCOURAGE (Trial 661-114)
- Enrollment was limited to only those patients who met strict inclusion criteria and elected to enroll
- Hypothesis testing was not planned or performed to compare SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and placebo for efficacy results in this trial; therefore, statistical significance cannot be determined
- Trial results are not included in the approved full Prescribing Information and the FDA did not consider this study in approving SYMDEKO

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Trial 661-114: Incidence of respiratory adverse events and safety results

Primary endpoint: Incidence of respiratory adverse events

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=7)

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>Wheezing</td>
<td>0</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Bronchospasm</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>Pre-dose</td>
<td>45.1 (16.2) n=48</td>
<td>48.0 (18.1) n=47</td>
</tr>
<tr>
<td>2 hours post-dose</td>
<td>-0.6 (2.1) n=45</td>
<td>0.3 (1.9) n=43</td>
</tr>
<tr>
<td>4 hours post-dose</td>
<td>-0.8 (4.3) n=45</td>
<td>0.0 (1.9) n=43</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.²³

- 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 1²¹

**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.

**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.

**Trial 661-114: Results for key and other secondary efficacy endpoints**

**Results for absolute and relative change in ppFEV₁²⁰**

- **KEY SECONDARY ENDPOINT**
  - **PERCENTAGE POINTS IMPROVEMENT VS PLACEBO** in absolute change in ppFEV₁ from baseline to the average of the Day 28 and Day 56 measurements (95% CI: 1.0, 4.4)
  - **SECONDARY ENDPOINT**
  - **PERCENTAGE IMPROVEMENT 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 SCORE²⁰**
  - **ADDITIONAL POINT IMPROVEMENT 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.²⁰

- 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)

**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—Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥ 2 x ULN), or AST or ALT ≥ 5 x ULN.
- Due to limited total exposure at the time of the interim analysis, rare adverse events may not have been detected.
- Study Design
- Study Population
- Key inclusion criteria:
  - Confirmed CF diagnosis and clinically stable
  - Patients ≥ 12 years of age (mean age 34.8 years)
  - Patients with F508del and a mutation predicted to be responsive to tezacaftor/ivacaftor
- 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, DTIGE, D1270N, E193K, E556K, F1052V, F1074L, K1060T, R74W.

**Endpoints**
- Primary endpoint: Mean absolute change in ppFEV1 from baseline to the average of Week 4 and Week 8 (please see page 22).11,22
- 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 24).11,22

**Study Population**
- Patients age 12 years and older with CF heterozygous for F508del and a mutation predicted to be responsive to tezacaftor/ivacaftor.
- Expansion 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—Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥ 2 x ULN), or AST or ALT ≥ 5 x ULN.

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- Primary endpoint: Mean absolute change in ppFEV1 from baseline to the average of Week 4 and Week 8 (please see page 22).11,22
- 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 24).11,22

**Study Population**
- Patients age 12 years and older with CF heterozygous for F508del and a mutation predicted to be responsive to tezacaftor/ivacaftor.
- Expansion 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—Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥ 2 x ULN), or AST or ALT ≥ 5 x ULN.

**Endpoints**
- Primary endpoint: Mean absolute change in ppFEV1 from baseline to the average of Week 4 and Week 8 (please see page 22).11,22
- 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 24).11,22

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, DTIGE, D1270N, E193K, E556K, F1052V, F1074L, K1060T, R74W.
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 weeks22

**Absolute Change in ppFEV1 in EXPAND**

**PRIMARY ENDPOINT**

6.8 **PERCENTAGE POINTS SIGNIFICANT 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)11

- 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), respectively22
- 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 analyses11,22

**OTHER EFFICACY ANALYSIS**

2.1 **PERCENTAGE POINTS SIGNIFICANT 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)11

- Improvements in patients with NPC1L1, compared to ivacaftor were 2.1 percentage points (95% CI: 1.2, 2.9, P<0.0001)11

**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.
- Co-administration of SYMDEKO with moderate CYP3A inducers, such as phenytoin, barbiturates, and some over-the-counter medications, may reduce therapeutic effectiveness.

**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.

**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)**

**VS PLACEBO**

11.1 **POINT SIGNIFICANT IMPROVEMENT**

from baseline to the average of Weeks 4 and 8 (95% CI: 8.7, 13.6; P<0.0001)

- 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.

**VS IVACAFTOR**

1.4 **POINT TREATMENT DIFFERENCE**

from baseline to the average of Weeks 4 and 8 (95% CI: -1.0, 3.9; not statistically significant)

**Results for CFQ-R Respiratory Domain Score in EXTEND Interim Analysis**

**EXTEND Interim Analysis: Improvements in CFQ-R were maintained for up to an additional 16 weeks with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**

**From EXPAND baseline up to Week 16 of EXTEND**

+9.9 **POINTS** within group in patients continuing on SYMDEKO

+11.0 **POINTS** within group in patients transitioning from ivacaftor to SYMDEKO

+10.8 **POINTS** within group in patients transitioning from placebo to SYMDEKO

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 21.

**IMPORTANT SAFETY INFORMATION**

- Pediatric Use
  - The safety and efficacy of SYMDEKO in patients with CF younger than 12 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%) SYMDEKO-treated patients 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

**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

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

Patients age 12 years and older, with a mutation predicted to be responsive to tezacaftor/ivacaftor
SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) safety profile demonstrated in clinical trials (cont)

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:

| Incidence of maximum transaminases during placebo-controlled trials
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ALT or AST</td>
<td>SYMDEKO (%)</td>
<td>Placebo (%)</td>
</tr>
<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>

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.

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

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.

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

Most common adverse reactions

Please click for additional 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.27

<table>
<thead>
<tr>
<th>Baseline ppFEV₁</th>
<th>SYMDEKO</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;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>40 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 (SYMDEKO range: 70 to 96.7; Placebo range: 70 to 96.2)</td>
<td>7.7% (11/142)</td>
<td>6.6% (10/152)</td>
</tr>
</tbody>
</table>

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

**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) vs placebo in a subset of patients age 12 to <18 years.

<table>
<thead>
<tr>
<th>Time point</th>
<th>SYMDEKO mean (SD)</th>
<th>PLACEBO mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY 1 Pre-dose</td>
<td>69.5 (13.8) n=51</td>
<td>68.9 (12.2) n=51</td>
</tr>
<tr>
<td>DAY 1 2 hours post-dose</td>
<td>0.0 (3.6) n=45</td>
<td>-0.5 (3.6) n=48</td>
</tr>
<tr>
<td>DAY 1 4 hours post-dose</td>
<td>0.4 (4.3) n=46</td>
<td>-0.5 (3.5) n=49</td>
</tr>
<tr>
<td>DAY 15 2 hours post-dose</td>
<td>0.4 (3.3) n=48</td>
<td>0.5 (3.9) n=46</td>
</tr>
<tr>
<td>DAY 15 4 hours post-dose</td>
<td>0.7 (5.1) n=46</td>
<td>0.4 (4.3) n=45</td>
</tr>
</tbody>
</table>

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; therefore, may have results for both SYMDEKO and placebo.

**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.

*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.*

SD, standard deviation.
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 (11.1)</td>
</tr>
</tbody>
</table>

• The majority of adverse events were considered mild or moderate in severity— Patients with adverse events by maximum severity: mild (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

3.2% of patients had adverse events leading to treatment discontinuation

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
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.

<table>
<thead>
<tr>
<th>Reduced blood levels of SYMDEKO expected with strong CYP3A Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>The concomitant use of CYP3A inducers may reduce SYMDEKO and ivacaftor blood levels, potentially resulting in reduced SYMDEKO efficacy. Co-administration of SYMDEKO with strong CYP3A inducers is not recommended.</td>
</tr>
</tbody>
</table>

Examples of strong CYP3A Inducers:
- Rifampin
- Rifabutin
- Phenobarbital
- St. John’s wort (Hypericum perforatum)

<table>
<thead>
<tr>
<th>Increased blood levels of SYMDEKO expected with strong or moderate CYP3A inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMDEKO dosing adjustment is recommended for co-administration with strong or moderate CYP3A inhibitors (see dose adjustments on following page).</td>
</tr>
</tbody>
</table>

Examples of strong CYP3A inhibitors:
- Ketoconazole
- Itraconazole
- Posaconazole

Examples of moderate CYP3A inhibitors:
- Fluconazole
- Erythromycin

<table>
<thead>
<tr>
<th>Increased exposure to these drugs may occur with SYMDEKO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole may inhibit CYP2C9 and increase exposures of these drugs.</td>
</tr>
</tbody>
</table>

Example of CYP2C9 substrate:
- Warfarin

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

Examples of P-gp substrates:
- Digoxin
- Cyclosporine
- Everolimus

<table>
<thead>
<tr>
<th>Drugs not expected to have a clinically significant effect on SYMDEKO or vice versa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caution and appropriate monitoring should be used with:</td>
</tr>
</tbody>
</table>
- Digoxin
- Cyclosporine
- Everolimus

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:
- 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 prescribed CF therapies with SYMDEKO.

<table>
<thead>
<tr>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tezacaftor 100 mg/ivacaftor 150 mg</td>
</tr>
<tr>
<td>Ivacaftor 150 mg</td>
</tr>
</tbody>
</table>

Dosing for hepatic impairment:

- Severe hepatic impairment (Child-Pugh Class C):
  - Tezacaftor 100 mg/ivacaftor 150 mg
  - Ivacaftor 150 mg

<table>
<thead>
<tr>
<th>Dosing for concomitant use with CYP3A Inducers or inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A Inducers</td>
</tr>
</tbody>
</table>
- CONCOMITANT USE NOT RECOMMENDED |

<table>
<thead>
<tr>
<th>Mild/moderate CYP3A inhibitors</th>
</tr>
</thead>
</table>
- Tezacaftor 100 mg/ivacaftor 150 mg |
- Ivacaftor 150 mg

| Strong CYP3A inhibitors |
- APPROXIMATELY 3-4 DAYS APART (into a week) |
- Tezacaftor 100 mg/ivacaftor 150 mg
- NO IVACAFTOR 150 mg DOSE

| Moderate CYP3A inhibitors |
- ALTERNATE TABLETS EVERY DAY |
- Tezacaftor 100 mg/ivacaftor 150 mg
- Ivacaftor 150 mg
- NO IVACAFTOR 150 mg DOSE

| Mild CYP3A inhibitors |
- Tezacaftor 100 mg/ivacaftor 150 mg |
- Ivacaftor 150 mg

Tablets are not actual size.
- 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 12 years of age have not been studied.

*Studies have not been conducted in patients with severe hepatic impairment.*
*After weighing the risks and benefits of treatment.*
*No dose adjustment is necessary.*
*Continue to alternate tablets every day.*
SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) missed doses and packaging

**Missed Dose**

**IF >6 HOURS**

- have passed since the missed morning or evening dose, the patient should not take the missed dose
- 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 (NDC 51167-661-01)
- SYMDEKO consists of a tezacaftor/ivacaftor fixed-dose combination tablet and an ivacaftor tablet
  - The tezacaftor/ivacaftor fixed-dose combination tablets are supplied as yellow, capsule-shaped tablets containing 100 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

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
CFTR modulator therapy for patients with CF age 12 years and older who have responsive mutations

**EVOLVE (Trial 1)**

**Patients homozygous for the F508del mutation**

**Lung function**

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

**EXPAND (Trial 2)**

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

**Lung function**

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

**Safety Results**

**Safety profile demonstrated in clinical trials**

- 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%) SYMDEKO-treated patients 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 26-27 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.

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

For more information, visit SYMDEKOhcp.com.