FOR PATIENTS WITH CF
WITH RESPONSIVE MUTATIONS

symdeko®
(tezacaftor/ivacaftor
and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

PROVIDING A CFTR-TARGETED THERAPY AS EARLY AS AGE 6 YEARS

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of cystic fibrosis (CF) in patients 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.

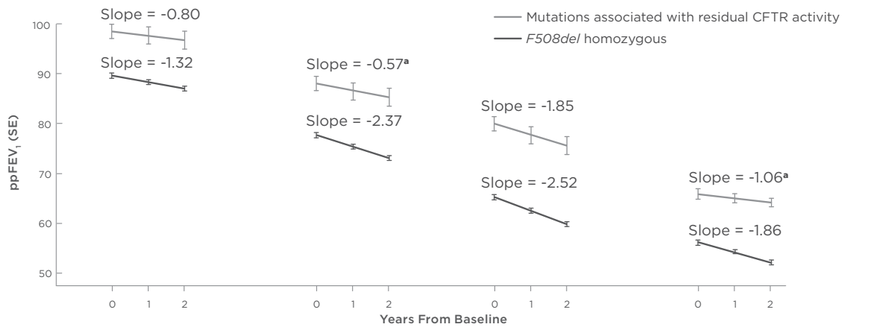
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

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

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[3,4]

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



Age Group	6-12	13-17	18-24	≥25
Residual CFTR Activity (n)	193	131	165	400
F508del (n)	4244	2195	2628	2849

Adapted from Sawicki GS, et al. Presented at the American Thoracic Society International Conference, Washington, DC, May 19-24, 2017. Poster A4847.

[a]*P*<0.001 vs *F508del*.

Study overview

Retrospective analysis of patients in the US CFFPR from 2006 to 2014. Objective was to characterize and compare rate of decline of $ppFEV_1$ in patients homozygous 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.

Pulmonary exacerbations significantly contribute to lung function decline[2,5-7]

- By age 12, **~30%** of patients will experience ≥1 pulmonary exacerbation(s) per year[2]
- In patients with CF, **52%** of FEV_1 decline is associated with pulmonary exacerbations[5,b]
- **25%** of patients do not recover to baseline FEV_1 within 3 months after treatment[6,c]
- Pulmonary exacerbations may have devastating effects on patients, including being associated with **subsequent reductions** in pulmonary function, which may be permanent[6,7]

[b]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. From 1997 to 2008, 851 patients were included, and 415 patients had at least 1 pulmonary exacerbation requiring hospitalization and antibiotics. Patients were followed for a median of 6.7 years.[5]

[c]A cohort study of patients age 6 years and older from the CFFPR. The objective of the study was to determine the proportion of patients who did 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.[6]

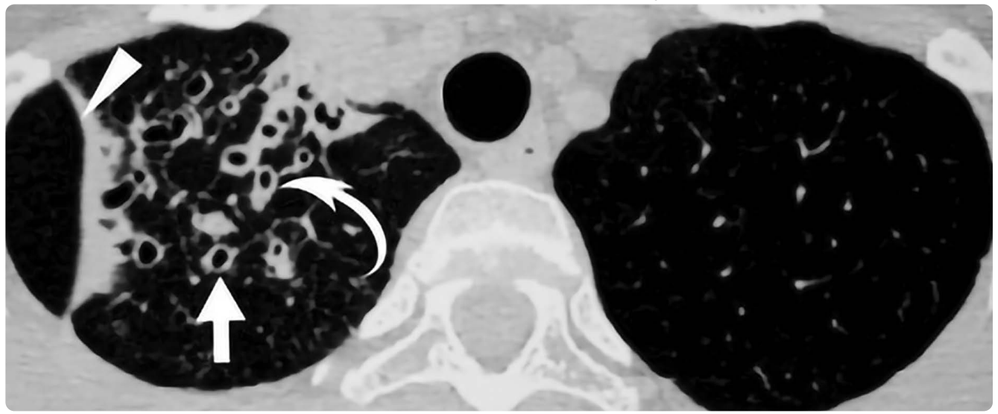
CFFPR, Cystic Fibrosis Foundation Patient Registry; FEV_1, forced expiratory volume in 1 second; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; SE, standard error.

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

Even patients who have normal $ppFEV_1$ may have evidence of structural lung damage[9,10]

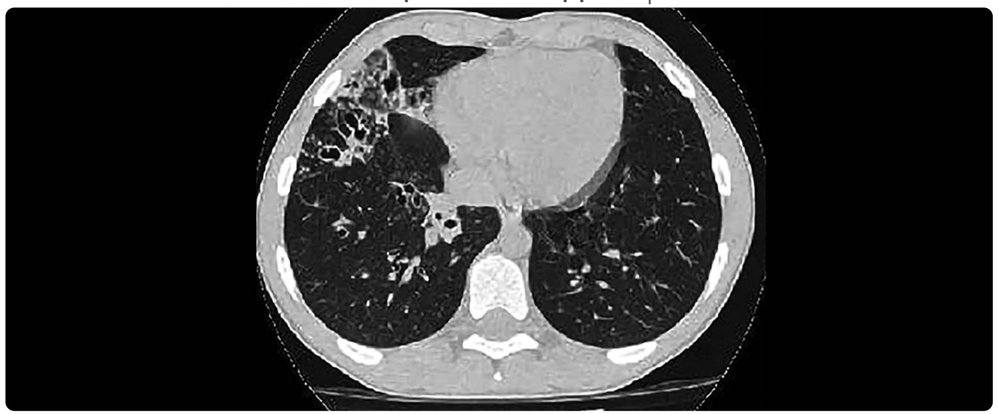
HRCT scans below show evidence of pulmonary abnormalities in 2 patients with CF with high $ppFEV_1$[10,11]

30-YEAR-OLD patient with $ppFEV_1$ of 94%[11,a]



Reprinted from *Chest*, 130(5), Judge EP et al. Pulmonary Abnormalities on High-Resolution CT Demonstrate More Rapid Decline Than FEV_1 in Adults With Cystic Fibrosis, 1424-1432, © 2006 with permission from Elsevier.

13-YEAR-OLD patient with $ppFEV_1$ of 96%[10,b]



Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis P.A. de Jong, Y. Nakano, M.H. Lequin, J.R. Mayo, R. Woods, P.D. Paré, H.A.W.M. Tiddens *European Respiratory Journal 23 (1) 93-97; DOI: 10.1183/09031936.03.00006603 Published 1 January 2003*

[a]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 30 with $ppFEV_1$ of 94%; HRCT shows moderate bronchiectasis (straight arrow), peribronchial wall thickening (curved arrow), and an apical bulla (arrowhead).[11]

[b]Case scenario of a patient from a 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 $ppFEV_1$ was 76.0%. All PFT scans were done within 1 month of HRCT scanning and HRCT scans were performed as part of routine checkups and, thus, patients were relatively stable. Image shows a patient at age 13 with $ppFEV_1$ 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.[10]

HRCT, high-resolution computed tomography; PFT, pulmonary function test.

For patients with CF age 6 years and older

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) targets CFTR protein defects in specific mutations[12]

CFTR Mutations That Produce CFTR Protein and Are Responsive to SYMDEKO[12-14]					
546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
*711+3A→G**	*E116K*	*G576A;R668C*†	*L967S*	*R117H*	*S737F*
*2789+5G→A**	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
*3272-26A→G**	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L**
*3849+10kbC→T**	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F**
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159P*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251N*
*A455E**	*F311del*	*H939R*	*M952I*	*R347H**	*S1255P*
A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036N*
A1067T	*F508C;S1251N*†	*I148T*	*P67L**	*R352Q**	*T1053I*
D110E	*F508del*^	*I175V*	*P205S*	*R352W*	*V201M*
*D110H**	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A;R668C†	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
*D579G**	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240G*
D614G	*G126D*	*I1027T*	*R31L*	*R1066H*	*V1293G*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070Q*	*W1282R*
D924N	*G178R*	*I1269N*	*R74W*	*R1070W**	*Y109N*
D979V	*G194R*	*I1366N*	*R74W;D1270N*†	*R1162L*	*Y161S*
*D1152H**	*G194V*	*K1060T*	*R74W;V201M*†	*R1283M*	*Y1014C*
D1270N	*G314E*	*L15P*	*R74W;V201M;D1270N*†	*R1283S*	*Y1032C*
E56K	*G551D*	*L206W**	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C**	*S549R*	

*Clinical data for these mutations in Clinical Studies [*see Clinical Studies in USPI (14.1 and 14.2)*].
^A patient must have 2 copies of the *F508del* mutation or at least 1 copy of a responsive mutation listed above in this table to be indicated for SYMDEKO.
†Complex/compound mutations in which a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Visit **SYMDEKOhcp.com** or refer to the full Prescribing Information to see which mutations are eligible

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of cystic fibrosis (CF) in patients 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

WARNINGS AND PRECAUTIONS

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF receiving 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

Hypersensitivity Reactions, Including Anaphylaxis

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

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

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with 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

USE IN SPECIFIC POPULATIONS

Pediatric Use

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

Please click for full Prescribing Information for SYMDEKO.

symdeko® (tezacaftor/ivacaftor and ivacaftor)

symdeko® (tezacaftor/ivacaftor and ivacaftor)

OVERVIEW OF CLINICAL TRIAL EXPERIENCE

	DESIGN	DOSING	MUTATIONS ENROLLED IN STUDY	REQUIRED ppFEV$_1$ AT SCREENING
IN PATIENTS AGE 6 THROUGH 11 YEARS **TRIAL 4** Homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation with a mutation predicted to be responsive to SYMDEKO[12] (see table on page 4 for a list of these mutations[a])	Phase 3, 24-week, open-label, multicenter study evaluating pharmacokinetics, safety, and tolerability[12,18]	• Tezacaftor/ivacaftor 50 mg/75 mg qd + ivacaftor 75 mg qd 12 hours apart (patients <40 kg, n=62)[18] • Tezacaftor/ivacaftor 100 mg/150 mg qd + ivacaftor 150 mg qd 12 hours apart (patients ≥40 kg, n=8)[18]	*F508del/F508del* or *F508del* plus 1 of the following: *3849+10kbC→T, R352Q, 3272-26A→G, 2789+5G→A, D1152H, L206W,* or *D579G*[16,18]	≥40% with a body weight of ≥15 kg without shoes[16]

[a]Patients do not need to have an *F508del* mutation if they have a mutation responsive to SYMDEKO to be indicated for SYMDEKO.[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. The FDA-approved dosing regimen for patients age 6 through 11 years weighing <30 kg is tezacaftor/ivacaftor (50 mg/75 mg qd + ivacaftor 75 mg qd) approximately 12 hours apart, and for patients weighing ≥30 kg it is tezacaftor/ivacaftor (100 mg/150 mg qd + ivacaftor 150 mg qd) approximately 12 hours apart.[12,18] See Limitations and Disclosures on next page.

IN PATIENTS AGE 12 YEARS AND OLDER **EVOLVE (TRIAL 1)** Homozygous for the *F508del* mutation in the *CFTR* gene[12]	Phase 3, 24-week, randomized, double-blind, placebo-controlled, 2-arm study evaluating efficacy and safety[19]	• Tezacaftor/ivacaftor 100 mg/150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=248)[19] • Placebo q12h (n=256)[19]	*F508del/F508del*[19]	≥40% and ≤90%[12]
EXPAND (TRIAL 2) Heterozygous for the *F508del* mutation with a mutation predicted to be responsive to SYMDEKO[12] (see table on page 4 for a list of these mutations[a])	Phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety[20]	• Tezacaftor/ivacaftor 100 mg/150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=161)[20] • Ivacaftor 150 mg q12h (n=156)[20] • Placebo q12h (n=161)[20]	*F508del* plus 1 of the following: *2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G, A455E, D110H, D1152H, D579G, E831X, L206W, P67L, R1070W, R117C, R347H, R352Q, S945L,* or *S977F*[12,21]	≥40% and ≤90%[12]

[a]Patients do not need to have an *F508del* mutation if they have a mutation responsive to SYMDEKO to be indicated for SYMDEKO.[12]

Additional mutations determined to be responsive to tezacaftor/ivacaftor based on *in vitro* data and eligible for but not enrolled in EXPAND were *A1067T, D110E, D1270N, E193K, E56K, F1052V, F1074L, K1060T,* and *R74W*.[12,21]

EXTEND (TRIAL 661-110) 96-week, open-label Extension Study of patients completing EVOLVE and EXPAND[15]	Phase 3, 96-week, open-label Extension Study evaluating safety, tolerability, and efficacy[15]	• Tezacaftor/ivacaftor 100 mg/150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=1042)[15]	• Efficacy set: Same as EVOLVE and EXPAND[15] • Safety set: Mutations from EVOLVE, EXPAND, and studies 103, 107, 109, and 111[15,a]	N/A

EXTEND 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 EXTEND[15]
- 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[15]
- 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[15]

EXTEND Limitations and Disclosures (cont'd)
- EXTEND may not meet the FDA definition of an adequate and well-controlled study due to its study design
- Trials required patients to remain on their usual prescribed CF regimen. In the Extension Study, patients may have had changes in their stable medication regimen, but the data set was not large enough to assess the effect that changes in concomitant drugs could have had on the efficacy and safety profile of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)
- Although a relatively large study over a 96-week period, rare adverse events might not have been detected
- Data from the Extension Study are not included in the full Prescribing Information for SYMDEKO and the FDA did not consider these data in approving the product

In all studies
- Selected exclusion criteria for all studies included 2 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; history of colonization with organisms associated with a more rapid decline in pulmonary status, such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*[12,16,17]
- Patients were required to take investigational treatment with fat-containing food in addition to their currently prescribed CF therapies[12]

ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

[a]Enrolled mutations for studies 103 and 111 were *F508del/F508del*; for study 107 (Trial 3), *F508del* with a mutation not responsive to tezacaftor/ivacaftor; and for study 109, *F508del* with a gating mutation or *R117H*. Trial 3 was terminated following the planned interim analysis because the pre-specified futility criteria were met.[12,15]
N/A, not applicable; q12h, every 12 hours; qd, once a day.

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

TRIAL 4
Patients with CF age 6 through 11 years, homozygous for *F508del* or heterozygous for *F508del* and a mutation predicted to be responsive to tezacaftor/ivacaftor[a]

Safety results through Week 24 were similar to those observed in patients age 12 years and older

Trial design

- **Phase 3, 24-week, open-label, multicenter study evaluating the pharmacokinetics, safety, and tolerability of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**[12,18]
- Patients (N=70) received tezacaftor/ivacaftor and ivacaftor. Dosage was based on weight[18]:
  - — <40 kg (n=62): tezacaftor/ivacaftor 50 mg/75 mg qd + ivacaftor 75 mg qd approximately 12 hours apart[18]
  - — ≥40 kg (n=8): tezacaftor/ivacaftor 100 mg/150 mg qd + ivacaftor 150 mg qd approximately 12 hours apart[18]
- Trial 4 was an open-label study with no placebo comparator arm[18]
- 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 Study[17,18]

Trial endpoints

- **Primary endpoint:** Safety and tolerability of SYMDEKO through Week 24 as determined by adverse events and clinical and laboratory assessments[18]
- **Select secondary endpoints:** Absolute change in sweat chloride from baseline through Week 4 and Week 24, absolute change in ppFEV$_1$ from baseline through Week 24, relative change in ppFEV$_1$ 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 from baseline through Week 24[18]

Trial 4 limitations and disclosures

- The study was open label and not placebo controlled; therefore, causality cannot be attributed to SYMDEKO

- 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[12,18]
- The dosing regimen studied in Trial 4 had a 40 kg weight-based dosing cutoff[18]
- The FDA-approved dosing regimen for patients age 6 through 11 years is[12]:
  - — <30 kg: tezacaftor/ivacaftor (50 mg/75 mg qd + ivacaftor 75 mg qd) approximately 12 hours apart
  - — ≥30 kg: tezacaftor/ivacaftor (100 mg/150 mg qd + ivacaftor 150 mg qd) approximately 12 hours apart

See page 21 for more information on Dosing and Administration.

[a]Enrolled mutations were *F508del* plus 1 of the following: *F508del*, *3849+10kbC→T*, *R352Q*, *3272-26A→G*, *2789+5G→A*, *D1152H*, *L206W*, and *D579G*.[16,18]

BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire-Revised.

Safety results through Week 24 were similar to those observed in patients age 12 years and older (cont'd)

TRIAL 4 PRIMARY ENDPOINT: SAFETY

Discontinuations[18]

- The proportion of patients who discontinued study drug due to adverse events was:

1.4% OF PATIENTS TREATED WITH SYMDEKO® (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 adverse events that led to treatment interruption; none were considered serious and all resolved[17,18]
  - — 2 were considered related or possibly related to study drug (blood creatine phosphokinase increased; ALT, AST, ALP, and GGT increased)

Transaminase Elevations[12,18]

Incidence of maximum transaminases	
Elevated ALT or AST	**SYMDEKO** (N=70) n (%)
>3 x ULN	**7 (10.0)[a]**
>5 x ULN	**3 (4.3)[b]**
>8 x ULN	**1 (1.4)**

[a]Includes all patients who experienced transaminase elevations >3 x ULN, including those who experienced >5 and >8 x ULN.[12]
[b]Includes all patients who experienced transaminase elevations >5 x ULN, including those who experienced >8 x ULN.[12]

- 1 patient experienced liver enzyme elevations that led to study drug interruption[18]
- 4 patients experienced total bilirubin >1 to ≤1.5 x ULN[17]
- No patients experienced total bilirubin >1.5 x ULN[18]

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)

TRIAL 4
Patients with CF age 6 through 11 years, homozygous for *F508del* or heterozygous for *F508del* and a mutation predicted to be responsive to tezacaftor/ivacaftor

Safety results through Week 24 were similar to those observed in patients age 12 years and older (cont'd)

- 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 21 and limitations and disclosures on page 8

TRIAL 4 PRIMARY ENDPOINT: SAFETY (cont'd)

Serious Adverse Events[18,a]

- Serious adverse events occurred in 6 patients (8.6%) on SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)
- Serious adverse events, which were not considered drug-related by the investigators, that occurred in patients treated with SYMDEKO included infective pulmonary exacerbation of CF, 2 (2.9%); breath odor, 1 (1.4%); snoring, 1 (1.4%); failure to thrive, 1 (1.4%); sinusitis, 1 (1.4%); and constipation, 1 (1.4%)

Most Common Adverse Events[18]

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

Adverse Reactions (Preferred Term)	**SYMDEKO** (N=70) n (%)
Cough	**25 (35.7)**
Infective pulmonary exacerbation of CF	**16 (22.9)**
Pyrexia	**13 (18.6)**
Abdominal pain	**10 (14.3)**
Nasal congestion	**10 (14.3)**
Rhinorrhea	**7 (10)**
Vomiting	**7 (10)**

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

Respiratory Adverse Events[18]

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

[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.[17]

Results for secondary endpoints: sweat chloride, lung function, BMI, and CFQ-R Respiratory Domain score

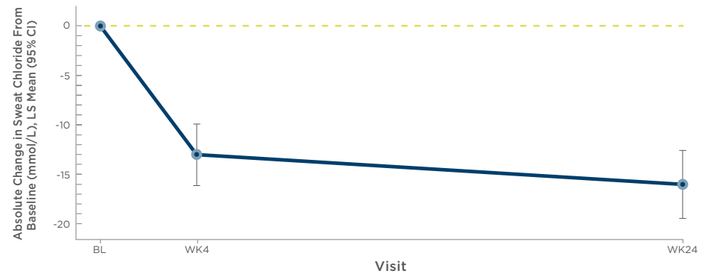
- Trial 4 was open label and not placebo controlled; therefore, causality cannot be attributed to SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

TRIAL 4 SECONDARY ENDPOINTS

Sweat Chloride[17,18]

- Reductions in sweat chloride were seen in the overall study population

Absolute Change in Sweat Chloride



-14.5 mmol/L REDUCTION through Week 24
(Baseline 99.1 mmol/L; 95% CI: -17.4, -11.6)

- Sweat chloride levels may not correlate with improvements in lung function ($ppFEV_1$)

Lung Function[18]

0.9 PERCENTAGE POINTS LS mean absolute change in $ppFEV_1$ from baseline **through Week 24**
(Baseline 91.1%; 95% CI: -0.6, 2.3)

1.4 PERCENT LS mean relative change in $ppFEV_1$ from baseline **through Week 24**
(Baseline 91.1%; 95% CI: -0.4, 3.1)

BMI[18]

+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)

CFQ-R Respiratory Domain Score (child version)[18]

3.4 POINT LS mean absolute change in CFQ-R Respiratory Domain score from baseline **through Week 24**
(95% CI: 1.4, 5.5)

- The CFQ-R Respiratory Domain score evaluated respiratory symptoms, including cough, sputum production, and difficulty breathing[22]

CI, confidence interval; LS, least squares.

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)

EVOLVE (TRIAL 1)/EXTEND

Patients with CF age 12 years and older, homozygous for the *F508del* mutation

Improvements in lung function in EVOLVE were generally maintained in EXTEND

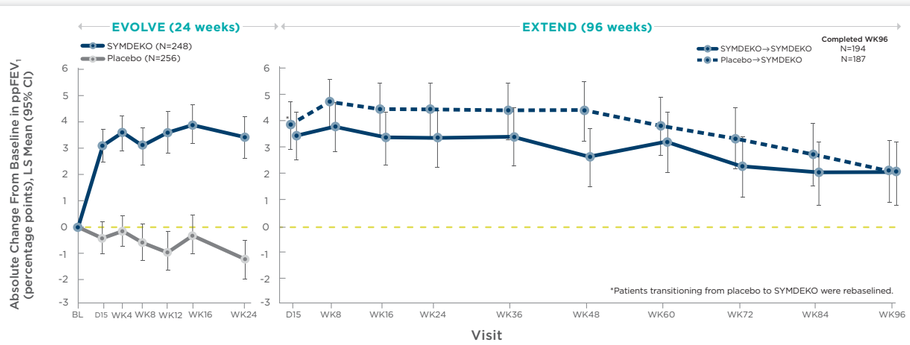
STUDY DESIGNS[12,19]

- **EVOLVE: Phase 3, 24-week, randomized, double-blind, placebo-controlled, 2-arm study evaluating efficacy and safety of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**
  - 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 $P \leq 0.05$[12,23]
  - The primary endpoint was mean absolute change in $ppFEV_1$ from baseline through Week 24[12]
  - Key secondary endpoints were relative change from baseline in $ppFEV_1$ 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 CFQ-R Respiratory Domain score from baseline through Week 24[12]
- **EXTEND: Phase 3, 96-week, open-label Extension Study of patients completing EVOLVE**[15]
  - The primary endpoint was the long-term safety and tolerability of SYMDEKO **(see page 19 for results)**; the secondary endpoint was long-term efficacy

LUNG FUNCTION

EVOLVE & EXTEND: Improvements in lung function were seen by Day 15 of EVOLVE and were generally maintained for an additional 96 weeks in EXTEND[12,15,19]

Absolute Change in $ppFEV_1$[12,15,19]



EVOLVE: SIGNIFICANT IMPROVEMENT IN PRIMARY ENDPOINT[12,19]

4.0 PERCENTAGE POINTS IMPROVEMENT vs PLACEBO in **LS mean absolute change** in $ppFEV_1$ from baseline **through Week 24** (95% CI: 3.1, 4.8; $P<0.0001$)

EVOLVE: SIGNIFICANT IMPROVEMENT IN KEY SECONDARY ENDPOINT[12,19]

6.8 PERCENT IMPROVEMENT vs PLACEBO in **LS mean relative change** in $ppFEV_1$ from baseline **through Week 24** (95% CI: 5.3, 8.3; $P<0.0001$)

Changes in $ppFEV_1$ from baseline vs placebo through Week 24[12,23,24,a]

Pre-specified subgroups by baseline $ppFEV_1$	LS mean absolute change in $ppFEV_1$ from baseline (percentage points)
(SYMDEKO n=23; placebo n=24; range 27.8% to <40%) **<40%**	**+3.5** (95% CI: 1.0, 6.1)
(SYMDEKO n=156; placebo n=152) **≥40 to <70%**	**+4.2** (95% CI: 3.1, 5.2)
(SYMDEKO n=66; placebo n=80; range ≥70% to 96.2%) **≥70%**	**+3.7** (95% CI: 2.2, 5.2)

[a]In EVOLVE, while $ppFEV_1$ at screening was 40-90%, changes may have occurred before baseline.[12,19]

PLEASE SEE PAGES 6 AND 7 FOR LIMITATIONS AND DISCLOSURES OF EXTEND.

Improvements in other key secondary endpoints were seen in 24 weeks of EVOLVE and persisted for up to an additional 96 weeks in EXTEND

	EVOLVE[12,19]	EXTEND[15]	
	SYMDEKO vs Placebo	SYMDEKO → SYMDEKO	Placebo → SYMDEKO
Pulmonary exacerbations[a]	**35% REDUCTION IN ESTIMATED EVENT RATE PER YEAR** **0.65 RATE RATIO** (95% CI: 0.48, 0.88) $P=0.0054$ Estimated event rate per year: 0.64 (78 events) for SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and 0.99 (122 events) for placebo through Week 24	**0.76** **ESTIMATED EVENT RATE** (423 events) during the 96-week analysis period (95% CI: 0.63, 0.92)	**0.68** **ESTIMATED EVENT RATE** (306 events) during the 96-week analysis period (95% CI: 0.55, 0.83)
LS mean absolute change from baseline in BMI	**+0.06 kg/m²** vs placebo at Week 24 (95% CI: -0.08, 0.19) **(not statistically significant)[b]**	**+0.38 kg/m²** within-group change from baseline at Week 96 (95% CI: 0.20, 0.55)	**+0.47 kg/m²** within-group change from baseline at Week 96 (95% CI: 0.30, 0.65)
LS mean absolute change from baseline in CFQ-R Respiratory Domain score[c]	**+5.1 POINTS** vs placebo through Week 24 (95% CI: 3.2, 7.0) **(not statistically significant)**	**+3.0 POINTS** within-group change from baseline at Week 96 (95% CI: 0.7, 5.3)	**+1.7 POINTS** within-group change from baseline at Week 96 (95% CI: -0.6, 4.0)

[a]Estimated event rate per year calculated using 48 weeks per year.[15,19]
[b]Placebo baseline BMI: 21.12 kg/m²; SYMDEKO baseline BMI: 20.96 kg/m².[19]
[c]The minimal clinically important difference (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.[25]

PLEASE SEE PAGES 6 AND 7 FOR LIMITATIONS AND DISCLOSURES OF EXTEND.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF receiving 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

Hypersensitivity Reactions, Including Anaphylaxis

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

A pulmonary exacerbation was defined as a change in antibiotic therapy (intravenous, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.[12]

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)

EXPAND (TRIAL 2)/EXTEND

Patients with CF age 12 years and older, heterozygous for *F508del* and a mutation predicted to be responsive to tezacaftor/ivacaftor[a]

Adding tezacaftor to ivacaftor led to improvement in lung function in EXPAND that was generally maintained in EXTEND

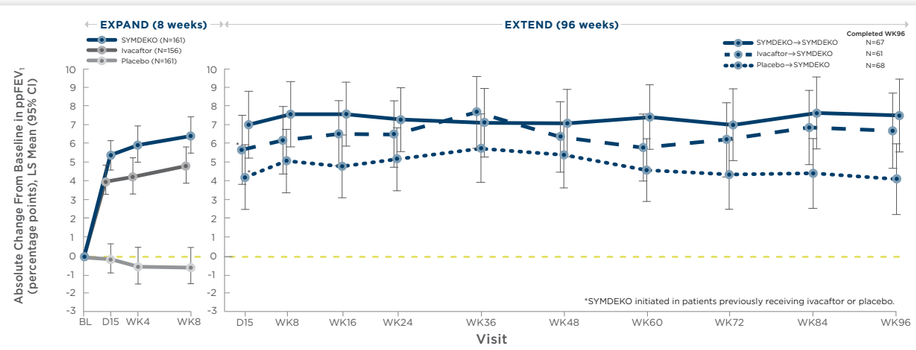
STUDY DESIGNS[12,20]

- **EXPAND: Phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor). This was a 2-period, 3-treatment, 8-week crossover study**
  - There were two 8-week dosing periods separated by an 8-week washout
  - The primary endpoint was the mean absolute change in ppFEV$_1$ from baseline to the average of Weeks 4 and 8
  - The key secondary endpoint was the absolute change in CFQ-R Respiratory Domain Score from baseline to the average of Weeks 4 and 8
- **EXTEND: 96-week, open-label Extension Study of patients completing EXPAND**[15]
  - The primary endpoint was the long-term safety and tolerability of SYMDEKO **(see page 19 for results)**; the secondary endpoint was long-term efficacy

LUNG FUNCTION

EXPAND & EXTEND: Improvements in lung function (ppFEV$_1$) were seen by Day 15 in EXPAND and were maintained in EXTEND[12,15,20]

Absolute Change in ppFEV$_1$[15,20]



EXPAND: SIGNIFICANT IMPROVEMENT IN PRIMARY ENDPOINT[12,20]

6.8 PERCENTAGE POINTS IMPROVEMENT vs PLACEBO in **LS mean absolute change** in ppFEV$_1$ from baseline **to the average of Weeks 4 and 8** (95% CI: 5.7, 7.8; *P*<0.0001)

EXPAND: SIGNIFICANT IMPROVEMENT IN OTHER EFFICACY ANALYSIS[12,20]

2.1 PERCENTAGE POINTS IMPROVEMENT vs IVACAFTOR in **LS mean absolute change** in ppFEV$_1$ from baseline **to the average of Weeks 4 and 8** (95% CI: 1.2, 2.9; *P*<0.0001)

- For individual mutations, changes in ppFEV$_1$ varied by genotype and ranged from -1.0 to 10.1; see full Prescribing Information for results by mutation. This was an ad hoc analysis[12,20]

[a]Enrolled mutations were: *2789+5G→A*, *3272-26A→G*, *3849+10kbC→T*, *711+3A→G*, *A455E*, *D110H*, *D1152H*, *D579G*, *E831X*, *L206W*, *P67L*, *R1070W*, *R117C*, *R347H*, *R352Q*, *S945L*, and *S977F*.[21]

PLEASE SEE PAGES 6 AND 7 FOR LIMITATIONS AND DISCLOSURES OF EXTEND.

Improvements vs placebo were seen in lung function subgroup analyses and CFQ-R Respiratory Domain score

EXPAND LUNG FUNCTION SUBGROUP ANALYSES

Changes in ppFEV$_1$ from baseline vs placebo to the average of Weeks 4 and 8[12,20,26,a]

Pre-specified subgroups by baseline ppFEV$_1$	LS mean absolute change in ppFEV$_1$ from baseline (percentage points)
(SYMDEKO n=16; placebo n=15; range 34.6% to <40%) **<40%**	**+4.4** (95% CI: 1.1, 7.8)
(SYMDEKO n=89; placebo n=95) **≥40 to <70%**	**+6.4** (95% CI: 5.1, 7.8)
(SYMDEKO n=54; placebo n=50; range ≥70% to 93.5%) **≥70%**	**+8.2** (95% CI: 6.4, 10.1)

[a]In EXPAND, while ppFEV$_1$ at screening was 40-90%, changes may have occurred before baseline.[12,20]

KEY SECONDARY ENDPOINT: CFQ-R RESPIRATORY DOMAIN SCORE

IN EXPAND TO THE AVERAGE OF WEEKS 4 AND 8[12,20,b]

+11.1 POINT SIGNIFICANT IMPROVEMENT VS PLACEBO in LS mean change from baseline (95% CI: 8.7, 13.6; *P*<0.0001)

+1.4 POINT TREATMENT DIFFERENCE VS IVACAFTOR in LS mean change from baseline (95% CI: -1.0, 3.9; **not statistically significant**)

IN EXTEND UP TO AN ADDITIONAL 96 WEEKS[15,b]

+13.8 POINTS LS mean within-group absolute change from baseline in patients **continuing on SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)** (95% CI: 10.3, 17.2)

+10.3 POINTS LS mean within-group absolute change from baseline in patients **transitioning from placebo to SYMDEKO** (95% CI: 7.0, 13.6)

+11.2 POINTS LS mean within-group absolute change from baseline in patients **transitioning from ivacaftor to SYMDEKO** (95% CI: 7.7, 14.7)

[b]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.[25]

- 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[12]

PLEASE SEE PAGES 6 AND 7 FOR LIMITATIONS AND DISCLOSURES OF EXTEND.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)

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

Safety data from 3 placebo-controlled clinical trials[12]

- The overall safety profile is based on data from 3 double-blind, placebo-controlled, Phase 3 clinical trials: 2 parallel-group trials of 12- and 24-week durations and 1 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 3 placebo-controlled Phase 3 trials, a total of 496 patients with CF aged 12 years and older received at least 1 dose of SYMDEKO
- The proportion of patients who **discontinued** study drug prematurely due to adverse events was:

1.6% OF PATIENTS TREATED WITH SYMDEKO

2.0% OF PATIENTS TREATED WITH PLACEBO

- The safety profile of SYMDEKO was generally similar across all subgroups of patients, including analysis by age, sex, baseline ppFEV$_1$, and geographic regions

Laboratory abnormalities: Transaminase elevations[12]

Incidence of maximum transaminases during placebo-controlled trials[12]

Elevated ALT or AST	SYMDEKO %	Placebo %
>3 X ULN	3.4	3.4
>5 X ULN	1.0	1.0
>8 X ULN	0.2	0.4

- The incidence of transaminase elevations was similar between treatment groups
- 1 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 (cont'd)

Cataracts[12]

- 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[12]

- 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[12]

Incidence of adverse reactions in ≥3% of patients taking SYMDEKO and greater than placebo (EVOLVE [Trial 1] and Trial 3*)[12]

Adverse Reactions (Preferred Term)	SYMDEKO (N=334) n (%)	Placebo (N=343) n (%)
Headache	49 (15)	44 (13)
Nausea	29 (9)	24 (7)
Sinus congestion	13 (4)	6 (2)
Dizziness	12 (4)	8 (2)

*Trial 3 was a 2-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.[12]

- 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.

symdeko® (tezacaftor/ivacaftor and ivacaftor)

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

Rates of respiratory adverse events[27,a]

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

Pooled analysis of respiratory events[27,a]

Respiratory Events	**SYMDEKO** (N=496) Patients with events, n (%)	**Placebo** (N=505) Patients with events, n (%)
Dyspnea	**30 (6.0)**	**36 (7.1)**
Respiration abnormal	**15 (3.0)**	**20 (4.0)**
Wheezing	**9 (1.8)**	**13 (2.6)**
Asthma	**4 (0.8)**	**6 (1.2)**
Chest discomfort	**3 (0.6)**	**3 (0.6)**
Bronchospasm	**2 (0.4)**	**4 (0.8)**
Bronchial hyperreactivity	**0**	**0**

[a]Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.[27]

Respiratory event rates by baseline ppFEV$_1$ subgroups[27,a]

Baseline ppFEV$_1$	**SYMDEKO** % (n/n)	**Placebo** % (n/n)
<40 (SYMDEKO range: 30.3 to <40; Placebo range: 27.8 to <40)	**14.3% (7/49)**	**27.9% (12/43)**
≥40 to **<70**	**12.5% (38/304)**	**16.8% (52/310)**
≥70 (SYMDEKO range: 70 to 96.7; Placebo range: 70 to 96.2)	**7.7% (11/142)**	**6.6% (10/152)**

[a]Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.[27]

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

EXTEND primary endpoint: long-term safety and tolerability up to 96 weeks

Safety results up to 96 weeks in EXTEND were consistent with those observed in placebo-controlled clinical trials[15]

1042 patients received ≥1 dose of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

- 253 patients (24.3%) were from parent studies that did not meet their primary endpoints[15]
- 682 patients completed the 96-week regimen; reasons for discontinuation included[15]:
  — 24 patients (3.0%) had adverse events that led to discontinuation. Those that occurred in ≥2 patients were AST and ALT increased (n=4), blood creatine phosphokinase increased (n=4), and infective pulmonary exacerbation of CF (n=2)
- 83 patients (10.5%) discontinued for other reasons[15]
- 2 deaths occurred after the treatment-emergent period: There was 1 death due to respiratory failure and influenza in a patient who had discontinued SYMDEKO 7 weeks prior and 1 death due to esophageal carcinoma in a patient who had discontinued SYMDEKO 6 weeks prior[28]
- Serious adverse events occurred in 351 patients (33.7%); those that occurred in ≥1% of patients included infective pulmonary exacerbation of CF in 243 patients (23.3%), hemoptysis in 25 patients (2.4%), and distal intestinal obstruction syndrome in 12 patients (1.2%)[15]
- 95.5% of patients (n=995) experienced at least 1 adverse event[15]
  — Patients with adverse events by maximum severity: mild (23.9%), moderate (53.0%), severe (18.3%), and life-threatening (0.3%)

Most common adverse events occurring in ≥10% of patients[15]

Preferred Term	**Safety Set** (N=1042) n (%)
Infective pulmonary exacerbation of cystic fibrosis	**549 (52.7)**
Cough	**374 (35.9)**
Nasopharyngitis	**227 (21.8)**
Sputum increased	**224 (21.5)**
Hemoptysis	**179 (17.2)**
Headache	**147 (14.1)**
Pyrexia	**136 (13.1)**
Oropharyngeal pain	**136 (13.1)**
Upper respiratory tract infection	**135 (13.0)**
Abdominal pain	**107 (10.3)**
Nausea	**107 (10.3)**
Diarrhea	**105 (10.1)**

- 6.1% of patients (n=63) had ALT and/or AST elevations >3 X ULN, 28 patients (2.7%) had elevations >5 x ULN, and 13 patients (1.3%) had elevations >8 x ULN[15]
  — 4 patients (0.4%) discontinued treatment due to both ALT and AST elevations[15]
- One patient had hypertransaminasemia, leading to treatment discontinuation[28]
- Respiratory events of special interest led to one treatment interruption and no treatment discontinuations[28]

symdeko® (tezacaftor/ivacaftor and ivacaftor)

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.

↓Reduced blood levels of SYMDEKO expected with strong CYP3A inducers[12]		
The concomitant use of CYP3A inducers may reduce tezacaftor and ivacaftor blood levels, potentially resulting in reduced SYMDEKO efficacy. **Co-administration of SYMDEKO with strong CYP3A inducers is not recommended**.		
Examples of strong CYP3A inducers	• Rifampin[a] • Rifabutin • Phenobarbital	• Carbamazepine • Phenytoin • St. John's wort (*Hypericum perforatum*)
↑Increased blood levels of SYMDEKO expected with strong or moderate CYP3A inhibitors[12]		
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[b] • Posaconazole	• Voriconazole • Telithromycin • Clarithromycin
Examples of moderate CYP3A inhibitors	• Fluconazole[c] • Erythromycin	**Avoid during treatment with SYMDEKO:** • Grapefruit
↑Increased exposure to these drugs may occur with SYMDEKO[12]		
Ivacaftor may inhibit CYP2C9 and increase exposures of CYP2C9 substrates.		
Examples of CYP2C9 substrates	**Monitor international normalized ratio of:** • Warfarin	**Use with caution:** • Glimepiride • Glipizide
SYMDEKO increased digoxin exposure and may increase exposure of other sensitive P-gp substrates.		
Examples of P-gp substrates	**Caution and appropriate monitoring should be used with:** • Digoxin • Cyclosporine • Everolimus	 • Sirolimus • Tacrolimus
↔Drugs not expected to have a clinically significant effect on SYMDEKO or vice versa[12,29]		
Examples of drugs not requiring dose adjustments	• Oral contraceptives (ethinyl estradiol/norethindrone) • Specific antidepressants (desipramine, citalopram, escitalopram, sertraline, mirtazapine, paroxetine, trazodone)	• Azithromycin • CYP3A substrates (eg, midazolam [oral]) • Ciprofloxacin • Pitavastatin (an OATP1B1 substrate)

[a]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.[12]
[b]Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure (AUC) by 4.0-fold and ivacaftor by 15.6-fold.[12]
[c]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.[12]
AUC, area under the curve; DDI, drug-drug interaction.

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[12]

- 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 age 6 through 11 years, weighing <30 kg	• Patients age 6 through 11 years, weighing ≥30 kg • Patients age 12 years and older
	Morning — 12 hours apart — Evening	Morning — 12 hours apart — Evening
Recommended Dose	 **Tezacaftor** 50 mg **Ivacaftor** 75 mg  **Ivacaftor** 75 mg	 **Tezacaftor** 100 mg **Ivacaftor** 150 mg  **Ivacaftor** 150 mg

Tablets are not actual size.

	Recommended Dose Adjustments Morning — 12 hours apart — Evening	
	Dosing for hepatic impairment[a]	
Severe hepatic impairment (Child-Pugh Class C)[b]	USE WITH CAUTION OR LESS FREQUENTLY[c] **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[d]	
Strong CYP3A inducers	CONCOMITANT USE NOT RECOMMENDED	CONCOMITANT USE NOT RECOMMENDED
Strong CYP3A inhibitors	APPROXIMATELY 3-4 DAYS APART (twice a week) **Tezacaftor/ivacaftor DOSE**	NO Ivacaftor DOSE
Moderate CYP3A inhibitors	ALTERNATE TABLETS EVERY DAY[e] DAY 1: **Tezacaftor/ivacaftor DOSE** DAY 2: **Ivacaftor DOSE**	NO Ivacaftor DOSE

[a]No dose adjustments are necessary for mild hepatic impairment.[12]
[b]Studies have not been conducted in patients with severe hepatic impairment.[12]
[c]Use with caution at an adjusted dose after weighing the risks and benefits of treatment.[12]
[d]No dose adjustment necessary for mild/moderate CYP3A inducers or mild CYP3A inhibitors.[12]
[e]Continue to alternate tablets every day.[12]

- Food or drink containing grapefruit should be avoided during treatment with SYMDEKO
- 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 effectiveness of SYMDEKO in patients with CF younger than 6 years of age have not been studied

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) packaging and missed dose information

Missed Dose[12]

IF ≤6 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

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[12]

- SYMDEKO is supplied in cartons containing 4 weekly blister cards, each with 14 tablets
- SYMDEKO is co-packaged with 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 white, 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 6 THROUGH 11 YEARS WEIGHING ≥30 KG AND PATIENTS AGE ≥12 YEARS

- 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

Remind patients that SYMDEKO should be taken as directed and discuss any necessary dose adjustments

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

CONSIDERATIONS FOR INITIATING PATIENTS PREVIOUSLY TREATED WITH ANOTHER CFTR MODULATOR

Transition information provided is not intended to imply clinical comparison between products.

- **KALYDECO® (ivacaftor)**
  Trial 2 (EXPAND), which evaluated SYMDEKO in comparison to KALYDECO, was not designed to demonstrate the safety or efficacy of transitioning to SYMDEKO and transitioning has not been evaluated in a clinical setting
- **ORKAMBI® (lumacaftor/ivacaftor)**
  SYMDEKO was not evaluated in comparison to ORKAMBI; nor has the safety or efficacy of transitioning to SYMDEKO from ORKAMBI been evaluated in a clinical setting

Considerations for transitioning patients are intended only for patients eligible for SYMDEKO. These are patients who are aged 6 years and older who are homozygous for the *F508del* mutation or who have at least one *CFTR* mutation that is responsive to tezacaftor/ivacaftor.[12]

Please click for Important Safety Information for SYMDEKO, KALYDECO, and ORKAMBI, and full Prescribing Information for SYMDEKO, KALYDECO, and ORKAMBI.

Transitioning patients from KALYDECO® (ivacaftor) to 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.

KALYDECO	SYMDEKO[12,30,31]
	• Patients age 6 through 11 weighing ≥30 kg or patients age 12 years and older will still be receiving the same amount of ivacaftor, but tezacaftor will be added with the transition to SYMDEKO
	• Patients age 6 through 11 and weighing <30 kg will be receiving 75 mg of ivacaftor twice a day (a lower amount), and tezacaftor will be added with the transition to SYMDEKO
	• **The initial dose of SYMDEKO should be taken in the morning, approximately 12 hours after the final dose of KALYDECO**
	• During approximately the first 2 weeks after transition:
	• **In patients age 6 through 11 and weighing ≥30 kg or age 12 years and older, blood levels of ivacaftor are expected to be maintained**
	• **In patients age 6 through 11 and weighing <30 kg, blood levels of ivacaftor are expected to decrease before establishing a new steady state**
	Blood levels of tezacaftor will be increasing in all patients
	Tezacaftor and ivacaftor are expected to reach steady state within 1-2 weeks

Selected drug-drug interactions to consider in patients transitioning from KALYDECO to SYMDEKO

- All recommendations in this brochure with regard to drug interactions for KALYDECO also apply to SYMDEKO, with the exception of the drugs listed below[30]
- 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 listed here and not the class[30]

Benzodiazepines alprazolam, diazepam, midazolam, and triazolam	• Caution and appropriate monitoring are recommended with KALYDECO[30,32] • No dose adjustments or additional monitoring is considered necessary with SYMDEKO[12,30]

SEE SYMDEKO DRUG-DRUG INTERACTIONS IN THE TABLE ON PAGE 20 AND DOSE ADJUSTMENTS ON PAGE 21.

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

kalydeco (ivacaftor) tablets 150 mg oral granules 5.8•13.4•25•50•75 mg

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO

INDICATIONS AND USAGE

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Transaminase (ALT or AST) Elevations

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

Hypersensitivity Reactions, Including Anaphylaxis

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

Concomitant Use With CYP3A Inducers

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

Cataracts

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

ADVERSE REACTIONS

Serious Adverse Reactions

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

Most Common Adverse Reactions

- The most common adverse reactions in the 221 patients treated with KALYDECO were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%)
- The safety profile for the CF patients enrolled in clinical trials (Trials 3-8) was similar to that observed in the 48-week, placebo-controlled trials (Trials 1 and 2)

USE IN SPECIFIC POPULATIONS

Pediatric Use

- The safety and effectiveness of KALYDECO in patients with CF younger than 1 month of age have not been established. The use of KALYDECO in children under the age of 1 month is not recommended
- Use of KALYDECO in patients aged 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated

Transitioning patients from ORKAMBI® (lumacaftor/ivacaftor) to 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.

ORKAMBI → SYMDEKO[12,30,31]

- Patients will still be receiving ivacaftor, but in combination with tezacaftor instead of lumacaftor
- **The initial dose of SYMDEKO should be taken in the morning, approximately 12 hours after the final dose of ORKAMBI**
- During approximately the first 2 weeks after transition:

Blood levels of lumacaftor will be decreasing

Blood levels of tezacaftor will be increasing

Blood levels of ivacaftor may decrease before establishing a new steady state

Tezacaftor and ivacaftor are expected to reach steady state within 1-2 weeks

- Based on pharmacokinetic modeling (which has not been directly evaluated in patients), ivacaftor exposures may decline slightly for a short period, but ivacaftor and either lumacaftor or tezacaftor exposures are expected to remain above their respective EC_{50} values throughout the transition period[30,31]
- During the first 1-2 weeks after transitioning, some lumacaftor-mediated CYP3A induction may remain, and interactions related to this should be considered[30]
- **When patients have no identified drug-drug interactions at the time of transition to SYMDEKO, consider waiting 2 weeks before initiating any new concomitant medications that interact with ORKAMBI as lumacaftor-mediated interactions may persist during this period**[30]

PLEASE SEE ADDITIONAL CONSIDERATIONS ON PAGES 27 AND 28.

EC_{50}, concentration of a drug that gives half-maximal response.

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 listed below and not the class. The table does not represent all possible drugs or drug classes that a patient could be receiving, and not all drug interactions with these products are shown.

The drug classes in the table below are organized by similar clinical considerations during transition. Because all drugs within a class may not have the same clinical considerations, some individual drugs within a class may be listed in different parts of the table.

Selected drug-drug interactions to consider when transitioning from ORKAMBI to SYMDEKO

Hormonal contraceptives should not be considered effective for at least 2 weeks after transition[30]	
Hormonal contraceptives ethinyl estradiol/ norethindrone	• Hormonal contraceptives should not be relied upon as an effective method of contraception when co-administered with ORKAMBI[33] • Hormonal contraceptives should not be considered effective for at least 2 weeks after transition[30] • SYMDEKO has no significant impact on hormonal contraceptives expected[12,34]
Consider waiting to use certain immunosuppressants for 2 weeks; if used after 2 weeks, caution and monitoring is recommended[30]	
Immunosuppressants cyclosporine, everolimus, sirolimus, and tacrolimus	• Co-administration of ORKAMBI is not recommended with these drugs • Due to residual CYP3A induction by lumacaftor with the potential to reduce drug exposures, consider waiting to initiate these drugs until 2 weeks after transition • After 2 weeks, no dose adjustment is necessary; caution is warranted and appropriate monitoring should be used
Consider waiting 2 weeks before using midazolam or triazolam[30]	
Benzodiazepines midazolam, triazolam (also see information on benzodiazepines on page 28)	• Co-administration with ORKAMBI is not recommended[33] • Due to residual CYP3A induction by lumacaftor with the potential to reduce drug exposures, consider waiting to initiate these drugs until 2 weeks after transition[30] • No dose adjustments of these drugs are recommended with SYMDEKO[12,34]
Consider waiting 2 weeks before starting certain antibiotics and antifungals; dose adjustment of SYMDEKO is recommended if used[30]	
Antibiotics clarithromycin, erythromycin, and telithromycin	• Co-administration with ORKAMBI may reduce the exposure and effectiveness of these drugs[33] - Consider an alternative to these antibiotics during concomitant use with ORKAMBI - Concomitant use of these antifungals with ORKAMBI is not recommended • Due to residual CYP3A induction by lumacaftor with the potential to reduce drug exposures, consider waiting to initiate these drugs until 2 weeks after transition[30] • Co-administration of strong and moderate CYP3A inhibitors, such as those listed, increased exposures to tezacaftor and ivacaftor. Dose adjustment of SYMDEKO is recommended; see the dosing and administration table on page 21[12]
Antifungals itraconazole, ketoconazole, posaconazole, and voriconazole (also see information on fluconazole on page 28)	

SEE SYMDEKO DRUG-DRUG INTERACTIONS IN THE TABLE ON PAGE 20 AND DOSE ADJUSTMENTS ON PAGE 21.

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

Transitioning patients from ORKAMBI® (lumacaftor/ivacaftor) to SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) (cont'd)

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

Selected drug-drug interactions to consider when transitioning from ORKAMBI to SYMDEKO (cont'd)

Dose adjustment of SYMDEKO recommended with fluconazole[30]	
Antifungals fluconazole	• No dose adjustments of ORKAMBI are recommended • Fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor and ivacaftor exposures • When co-administered with fluconazole and other moderate CYP3A inhibitors, the dose of SYMDEKO should be reduced; see the dosing and administration table on page 21
Drugs whose dosage may have been increased during ORKAMBI treatment: Consider dose reduction during the transition if dosage of any drug below was increased during treatment with ORKAMBI[30]	
Antidepressants citalopram, escitalopram, mirtazapine, paroxetine, sertraline, and trazodone **Anti-inflammatories** ibuprofen **Benzodiazepines** alprazolam, diazepam **Oral hypoglycemics** repaglinide, nateglinide **Proton pump inhibitors (PPIs) and H2 blockers** esomeprazole, lansoprazole, omeprazole, and ranitidine **Systemic corticosteroids** methylprednisolone, prednisone, and prednisolone	• ORKAMBI may reduce or alter the exposure of these drugs, which may require a higher dose during co-administration to obtain desired clinical effect • Lumacaftor-mediated CYP3A induction will decrease as ORKAMBI exposure decreases. For patients whose doses of these medications were increased during co-administration with ORKAMBI, the exposure of these concomitant medications may increase if dose is held constant during transition to SYMDEKO • A dose reduction of the concomitant drug, as appropriate, should be considered at the time of transition • No dose adjustments of these drugs are recommended during treatment with SYMDEKO
Patients should now avoid grapefruit[12,33]	
Food/drink grapefruit	• Advise patients to avoid grapefruit products during the first week after treatment initiation with ORKAMBI • Co-administration of SYMDEKO with food or drink containing grapefruit, which contains one or more components that moderately inhibit CYP3A, may increase exposure of tezacaftor and ivacaftor • Food or drink containing grapefruit should be avoided during treatment with SYMDEKO
No action needed during transition with montelukast, which may be affected by ORKAMBI[29,33]	
Anti-allergics montelukast	• ORKAMBI may decrease the exposure of montelukast, which may reduce its efficacy. No dose adjustment is recommended, appropriate clinical monitoring as is reasonable • During the first 2 weeks following SYMDEKO initiation, exposure to montelukast may be reduced during co-administration. Continue appropriate clinical monitoring through 2 weeks after the transition as is reasonable • No dose adjustments of montelukast or SYMDEKO are recommended
Other drug interactions are predicted with ORKAMBI and/or SYMDEKO, including[29]**:**	
• Antiarrhythmics (digoxin) • Anticoagulants (warfarin)	• Anticonvulsants (carbamazepine, phenobarbital, phenytoin) • Herbals (St. John's wort)

PLEASE SEE ADDITIONAL INFORMATION REGARDING THESE INTERACTIONS ON PAGE 20.

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

INDICATION AND IMPORTANT SAFETY INFORMATION FOR ORKAMBI

INDICATION AND USAGE

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.

Limitations of Use

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Use in Patients With Advanced Liver Disease

- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI. Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced

Liver-related Events

- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve
- Dosing should be interrupted in patients with ALT or AST >5 x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations >3 x ULN when associated with bilirubin elevations >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

Hypersensitivity Reactions, Including Anaphylaxis

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

Respiratory Events

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted FEV_1 ($ppFEV_1$) <40). Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

Effect on Blood Pressure

- Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI

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

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

IMPORTANT SAFETY INFORMATION FOR ORKAMBI (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Drug Interactions

- Substrates of CYP3A

  Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended. ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI

- Strong CYP3A Inducers

  Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended

Cataracts

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

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients

Most Common Adverse Reactions

- The most common adverse reactions in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza
- The safety profile in patients age 6 through 11 years from an open-label trial (Trial 3; N=58) and a placebo-controlled trial (Trial 4; patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and sputum increased
- The safety profile in patients age 2 through 5 years from an open-label trial (Trial 6; N=60) was similar to that in patients aged 6 years and older. The safety profile in patients age 1 through 2 years from an open-label trial (Trial 7; N=46) was similar to that in patients aged 2 years and older

USE IN SPECIFIC POPULATIONS

Pediatric Use

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

References: 1. Welsh MJ, Ramsey BW, Accurso F, Cutting GR. Cystic fibrosis: membrane transport disorders. In: Valle D, Beaudet A, Vogelstein B, et al, eds. *The Online Metabolic & Molecular Bases of Inherited Disease*. The McGraw-Hill Companies Inc; 2004: part 21, chap 201. www.ommbid.com. **2.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2018*. Bethesda, MD: Cystic Fibrosis Foundation; 2019 . **3.** Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros*. 2010;9(4):250-256. **4.** Sawicki GS, Konstan MW, McKone EF, et al. Rate of lung function decline in patients with cystic fibrosis (CF) having a residual function gene mutation. Presented at: the American Thoracic Society International Conference; May 19-24, 2017; Washington, DC. **5.** Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir J*. 2012;40(1):61-66. **6.** Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med*. 2010;182(5):627-632. **7.** Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV_1 decline in both adults and children with cystic fibrosis. *Pediatr Pulmonol*. 2011;46(4):393-400. **8.** Farrell PM, Li Z, Kosorok MR, et al. Longitudinal evaluation of bronchopulmonary disease in children with cystic fibrosis. *Pediatr Pulmonol*. 2003;36(3):230-240. **9.** Ellemunter H, Fuchs SI, Unsinn KM, et al. Sensitivity of lung clearance index and chest computed tomography in early CF lung disease. *Respir Med*. 2010;104(12):1834-1842. **10.** de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J*. 2004;23(1):93-97. **11.** Judge EP, Dodd JD, Masterson JB, Gallagher CG. Pulmonary abnormalities on high-resolution CT demonstrate more rapid decline than FEV_1 in adults with cystic fibrosis. *Chest*. 2006;130(5):1424-1432. **12.** SYMDEKO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2023. **13.** The Clinical and Functional TRanslation of CFTR (CFTR2); available at http://cftr2.org. List of CFTR2 mutations. https://cftr2.org/mutations_history/CFTR2_29April2022.xlsx. Accessed May 9, 2023. **14.** National Center for Biotechnology Information. ClinVar. Available at https://www.ncbi.nlm.nih.gov/clinvar/. Accessed May 9, 2023. **15.** Flume P, Biner RF, Downey DG, et al. An open-label extension study of tezacaftor/ivacaftor in patients aged ≥12 years with cystic fibrosis homozygous for *F508del-CFTR* or heterozygous for *F508del-CFTR* and a residual function mutation. Presented at: the North American Cystic Fibrosis Conference; October 31-November 2, 2019; Nashville, TN. **16.** Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *J Cyst Fibros.* 2019;18(5)(suppl 1-10):708-713. **17.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-2254; 2019. **18.** Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *J Cyst Fibros.* 2019;18(5):708-713. **19.** Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for *Phe508del. N Engl J Med.* 2017;377(21):2013-2023. **20.** Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med.* 2017;377(21):2024-2035. **21.** Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med.* 2017;377(21)(suppl 1-25):2024-2035. **22.** CFQ-R Cystic Fibrosis Questionnaire-REVISED. Cystic Fibrosis Foundation. Quittner, Modi, Watrous and Messer, 2000. Revised 2002. CFQ-R—Children, English Version 2.0. **23.** Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for *Phe508del. N Engl J Med.* 2017;377(21)(suppl 1-29): 2013-2023. **24.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-0258 (v2.0); 2019. **25.** Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic pseudomonas aeruginosa airway infection. *Chest.* 2009;135(6):1610-1618. **26.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-0009 (v2.0); 2019. **27.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-0004 (v2.0); 2019. **28.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-4762 (v1.0); 2019. **29.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-10745 (v1.0); 2021. **30.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-10552 (v1.0); 2021. **31.** Wu SP, Garg V, Tsai A, et al. Sustained CFTR correction and potentiation is predicted during transitions between lumacaftor/ivacaftor and tezacaftor/ivacaftor-based regimens. Poster presented at: the 31st Annual North American Cystic Fibrosis Conference; November 2-4, 2017; Indianapolis, IN. **32.** KALYDECO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2023. **33.** ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2023. **34.** Garg V, Shen J, Li C, et al. Drug-drug interaction profile of tezacaftor/ivacaftor (TEZ/IVA) in healthy adult subjects. Poster presented at: 31st Annual North American Cystic Fibrosis Conference; November 2-4, 2017; Indianapolis, IN.

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

symdeko®
(tezacaftor/ivacaftor and ivacaftor)

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

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

CFTR-TARGETED THERAPY CAN BEGIN AS EARLY AS AGE 6 YEARS

IN PATIENTS AGE 12 YEARS AND OLDER

EVOLVE (Trial 1) — **Patients age 12 years and older homozygous for the *F508del* mutation**[12,19]

Patients age 12 years and older heterozygous for *F508del* with a mutation predicted to be responsive to tezacaftor/ivacaftor[12,20] — **EXPAND** (Trial 2)

SIGNIFICANT IMPROVEMENTS IN LUNG FUNCTION

4.0 PERCENTAGE POINTS IMPROVEMENT VS PLACEBO
in mean absolute change in ppFEV$_1$ from baseline through Week 24 (95% CI: 3.1, 4.8; *P*<0.0001)

6.8 PERCENTAGE POINTS IMPROVEMENT VS PLACEBO
in mean absolute change in ppFEV$_1$ from baseline to the average of Weeks 4 and 8 (95% CI: 5.7, 7.8; *P*<0.0001)

IMPROVEMENTS SEEN IN EVOLVE AND EXPAND WERE GENERALLY MAINTAINED UP TO 96 WEEKS IN EXTEND[15]

Safety Results — **Safety profile demonstrated in clinical trials**[12,a]

- 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[b]) 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 ULN 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
- Safety results up to 96 weeks in EXTEND were consistent with those observed in placebo-controlled clinical trials[15]
- **See pages 16-19 for additional safety profile information**

[a]Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.[12]
[b]Trial 3 was a 2-arm study that compared SYMDEKO to placebo in patients with CF age 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.[12]

IN PATIENTS AGE 6 THROUGH 11 YEARS

TRIAL 4 — **Patients age 6 through 11 years who are homozygous or heterozygous for the *F508del* mutation or have a mutation predicted to be responsive to SYMDEKO**[12]

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

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

VERTEX