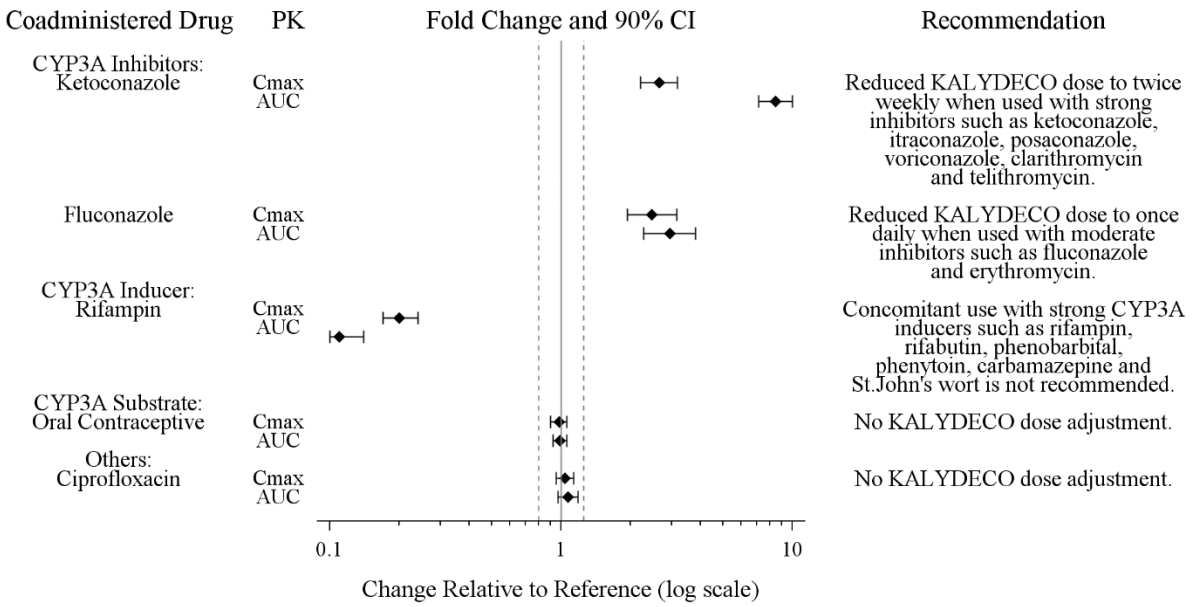
Figure 3: Impact of Other Drugs on KALYDECO



Note: The data obtained for KALYDECO without co-administration of inducers or inhibitors are used as reference. The vertical lines are at 0.8, 1.0, and 1.25, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess carcinogenic potential of KALYDECO. No evidence of tumorigenicity was observed in mice or rats at ivacaftor oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equal to 1 and 4 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (yielding exposures approximately 8 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its major metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its major metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (yielding exposures approximately 6 and 3 times, respectively, the MRHD based on summed AUCs of ivacaftor and its major metabolites).

14 CLINICAL STUDIES

14.1 Trials in Patients with CF who have a *G551D* Mutation in the *CFTR* Gene

Dose Ranging:

Dose ranging for the clinical program consisted primarily of one double-blind, placebo-controlled, crossover trial in 39 adult (mean age 31 years) Caucasian patients with CF who had FEV_1 ≥40% predicted. Twenty patients with median predicted FEV_1 at baseline of 56% (range: 42% to 109%) received KALYDECO 25, 75, 150 mg or placebo every 12 hours for 14 days and 19 patients with median predicted FEV_1 at baseline of 69% (range: 40% to 122%) received KALYDECO 150, 250 mg, or placebo every 12 hours for 28 days. The selection of the 150 mg every 12 hours dose was primarily based on nominal improvements in lung function (pre-dose FEV_1) and changes in pharmacodynamic parameters (sweat chloride and nasal potential difference). The twice-daily dosing regimen was primarily based on an apparent terminal plasma half-life of approximately 12 hours.

Efficacy:

The efficacy of KALYDECO in patients with CF who have a *G551D* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving KALYDECO 150 mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study.

Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age 26 years) with FEV_1 at screening between 40-90% predicted [mean FEV_1 64% predicted at baseline (range: 32% to 98%)]. Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with FEV_1 at screening between 40-105% predicted [mean FEV_1 84% predicted at baseline (range: 44% to 134%)]. Patients who had persistent *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded.

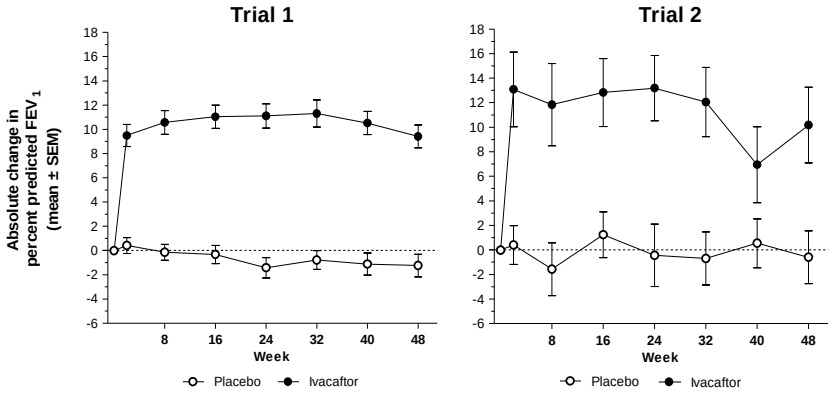
Patients in both trials were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV_1 through 24 weeks of treatment.

In both studies, treatment with KALYDECO resulted in a significant improvement in FEV_1. The treatment difference between KALYDECO and placebo for the mean absolute change in percent predicted FEV_1 from baseline through Week 24 was 10.6 percentage points (P<0.0001) in Trial 1 and 12.5 percentage points (P<0.0001) in

Trial 2 (Figure 4). These changes persisted through 48 weeks. Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, and geographic region.

Figure 4: Mean Absolute Change from Baseline in Percent Predicted FEV_1 *



* Primary endpoint was assessed at the 24-week time point.

Other efficacy variables included absolute change from baseline in sweat chloride *[see Clinical Pharmacology (12.2)]*, time to first pulmonary exacerbation (Trial 1 only), absolute change from baseline in weight, and improvement from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing. For the purpose of the study, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. Patients treated with KALYDECO demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight (Table 5). Weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, were consistent with absolute change from baseline in weight.

Table 5: Effect of KALYDECO on Other Efficacy Endpoints in Trials 1 and 2

	Trial 1		Trial 2	
Endpoint	**Treatment difference [a] (95% CI)**	***P* value**	**Treatment difference [a] (95% CI)**	***P* value**
Mean absolute change from baseline in CFQ-R respiratory domain score (points)				
Through Week 24	8.1 (4.7, 11.4)	<0.0001	6.1 (-1.4, 13.5)	0.1092
Through Week 48	8.6 (5.3, 11.9)	<0.0001	5.1 (-1.6, 11.8)	0.1354
Relative risk of pulmonary exacerbation				
Through Week 24	0.40 [b]	0.0016	NA	NA
Through Week 48	0.46 [b]	0.0012	NA	NA
Mean absolute change from baseline in body weight (kg)				
At Week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
At Week 48	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002
Absolute change in sweat chloride (mmol/L)				
Through Week 24	-48 (-51, -45)	<0.0001	-54 (-62, -47)	<0.0001
Through Week 48	-48 (-51, -45)	<0.0001	-53 (-61, -46)	<0.0001

CI: confidence interval; NA: not analyzed due to low incidence of events
[a] Treatment difference = effect of KALYDECO – effect of Placebo
[b] Hazard ratio for time to first pulmonary exacerbation

14.2 Trial in Patients with a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* Mutation in the *CFTR* Gene

The efficacy and safety of KALYDECO in patients with CF who have a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene were evaluated in a two-part, randomized, double-blind, placebo-controlled, crossover design clinical trial in 39 patients with CF (Trial 4). Patients who completed Part 1 of this trial continued into the 16-week open-label Part 2 of the study. The mutations studied were *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P*, and *G1349D.* See *Clinical Studies (14.1)* for efficacy in patients with a *G551D* mutation.

Patients were 6 years of age or older (mean age 23 years) with FEV_1 ≥40% at screening [mean FEV_1 at baseline 78% predicted (range: 43% to 119%)]. Patients with evidence of colonization with *Burkholderia cenocepacia, Burkholderia dolosa,* or *Mycobacterium abscessus* and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal at screening were excluded.

Patients were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 8 weeks in addition to their prescribed CF therapies during the first treatment period and crossed over to the other treatment for the second 8 weeks. The two 8-week treatment periods were separated by a 4- to 8-week washout period. The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 8 weeks of treatment. Other efficacy variables included absolute change from baseline in sweat chloride through 8 weeks of treatment *[see Clinical Pharmacology (12.2)],*

absolute change from baseline in body mass index (BMI) at 8 weeks of treatment (including body weight at 8 weeks), and improvement in CFQ-R respiratory domain score through 8 weeks of treatment. For the overall population of the 9 mutations studied, treatment with KALYDECO compared to placebo resulted in significant improvement in percent predicted FEV_1 [10.7 through Week 8 (P<0.0001)], BMI [0.66 kg/m^2 at Week 8 (P<0.0001)], and CFQ-R respiratory domain score [9.6 through Week 8 (P=0.0004)]; however, there was a high degree of variability of efficacy responses among the 9 mutations (Table 6).

Table 6: Effect of KALYDECO for Efficacy Variables in the Overall Populations and for Specific *CFTR* Mutations

Mutation (n)	Absolute change in percent predicted FEV_1			BMI (kg/m^2)	CFQ-R Respiratory Domain Score (Points)	Absolute Change in Sweat Chloride (mmol/L)
	At Week 2	At Week 4	At Week 8	At Week 8	At Week 8	At Week 8
All patients (n=39) Results shown as mean (95% CI) change from baseline KALYDECO vs. placebo-treated patients:						
	8.3 (4.5, 12.1)	10.0 (6.2, 13.8)	13.8 (9.9, 17.6)	0.66 † (0.34, 0.99)	12.8 (6.7, 18.9)	-50 (-58, -41) *
Patients grouped under mutation types (n) Results shown as mean (minimum, maximum) for change from baseline for KALYDECO-treated patients **:						
G1244E (5)	11 (-5, 25)	6 (-5, 13)	8 (-1, 18)	0.63 (0.34, 1.32)	3.3 (-27.8, 22.2)	-55 (-75, -34)
G1349D (2)	19 (5, 33)	18 (2, 35)	20 (3, 36)	1.15 (1.07, 1.22)	16.7 (-11.1, 44.4)	-80 (-82, -79)
G178R (5)	7 (1, 17)	10 (-2, 21)	8 (-1, 18)	0.85 (0.33, 1.46)	20.0 (5.6, 50.0)	-53 (-65, -35)
G551S (2)	0 (-5, 5)	0.3 (-5, 6)	3 ††	0.16 ††	16.7 ††	-68 ††
G970R (4)	7 (1, 13)	7 (1, 14)	3 (-1, 5)	0.48 (-0.38, 1.75)	1.4 (-16.7, 16.7)	-6 (-16, -2)
S1251N (8)	2 (-23, 20)	8 (-13, 26)	9 (-20, 21)	0.73 (0.08, 1.83)	23.3 (5.6, 50.0)	-54 (-84, -7)
S1255P (2)	11 (8, 14)	9 (5, 13)	3 (-1, 8)	1.62 (1.39, 1.84)	8.3 (5.6, 11.1)	-78 (-82, -74)
S549N (6)	11 (5, 16)	8 (-9, 19)	11 (-2, 20)	0.79 (0.00, 1.91)	8.8 (-8.3, 27.8)	-74 (-93, -53)
S549R (4)	3 (-4, 8)	4 (-4, 10)	5 (-3, 13)	0.53 (0.33, 0.80)	6.9 (0.0, 11.1)	-61 ††† (-71, -54)

* n=36 for the analysis of absolute change in sweat chloride.
** Statistical testing was not performed due to small numbers for individual mutations.
† Result for weight gain as a component of body mass index was consistent with BMI.
†† Reflects results from the one patient with the *G551S* mutation with data at the 8-week time point.
††† n=3 for the analysis of absolute change in sweat chloride.

14.3 Trial in Patients with CF who have an *R117H* Mutation in the *CFTR* Gene

The efficacy and safety of KALYDECO in patients with CF who have an *R117H* mutation in the *CFTR* gene were evaluated in a randomized, double-blind, placebo-controlled, parallel-group clinical trial (Trial 5). Fifty-nine of 69 patients completed 24 weeks of treatment. Two patients discontinued and 8 patients did not complete treatment due to study termination. Trial 5 evaluated 69 clinically stable patients with CF who were 6 years of age or older (mean age 31 years). Patients who were 12 years and older had FEV_1 at screening between 40-90% predicted, and patients who were 6-11 years of age had FEV_1 at screening between 40-105% predicted. The overall mean FEV_1 was 73% predicted at baseline (range: 33% to 106%). The patients had well preserved BMIs (mean overall: 23.76 kg/m^2) and a high proportion were pancreatic sufficient as assessed by a low rate of pancreatic enzyme replacement therapy use (pancreatin: 11.6%; pancrelipase: 5.8%). Patients who had persistent *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening, and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the ULN, were excluded.

Patients were randomized 1:1 to receive either 150 mg of KALYDECO (n=34) or placebo (n=35) every 12 hours with food containing fat for 24 weeks in addition to their prescribed CF therapies.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment. The treatment difference for absolute change in percent predicted FEV_1 through Week 24 was 2.1 percentage points (analysis conducted with the full analysis set which included all 69 patients), and did not reach statistical significance (Table 7).

Other efficacy variables that were analyzed included absolute change in sweat chloride from baseline through Week 24, improvement in cystic fibrosis respiratory symptoms through Week 24 as assessed by the CFQ-R respiratory domain score (Table 7), absolute change in body mass index (BMI) at Week 24, and time to first pulmonary exacerbation. The overall treatment difference for the absolute change from baseline in BMI at Week 24 was 0.3 kg/m^2 and the calculated hazard ratio for time to first pulmonary exacerbation was 0.93, which were not statistically significant.

Statistically significant improvements in clinical efficacy (FEV_1, CFQ-R respiratory domain) were seen in several subgroup analyses, and decreases in sweat chloride were observed in all subgroups. The mean baseline sweat chloride for all patients was 70 mmol/L. Subgroups analyzed included those based on age, lung function, and poly-T status (Table 7).

Table 7: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) and in Relevant Subgroups Through 24 Weeks

		Absolute Change through Week 24 *- All Randomized Patients								
		% Predicted FEV_1 (Percentage Points)			CFQ-R Respiratory Domain Score (Points)			Sweat Chloride (mmol/L)		
Subgroup Parameter	Study Drug	n	Mean	Treatment Difference (95% CI)	n	Mean	Treatment Difference (95% CI)	n	Mean	Treatment Difference (95% CI)
R117H–All Patients										
	Placebo	35	0.5	2.1	34	-0.8	8.4	35	-2.3	-24.0
	KALYDECO	34	2.6	(-1.1, 5.4)	33	7.6	(2.2, 14.6)	32	-26.3	(-28.0, -19.9)
Subgroup by Age										

Table 7: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) and in Relevant Subgroups Through 24 Weeks

		Absolute Change through Week 24 *- All Randomized Patients								
6-11	Placebo	8	3.5	-6.3	7	-1.6	-6.1	8	1.0	-27.6
	KALYDECO	9	-2.8	(-12.0, -0.7)	8	-7.7	(-15.7, 3.4)	8	-26.6	(-37.2, -18.1)
12-17	Placebo	1			1			1		
	KALYDECO	1	---	---	1	---	---	1	---	---
≥18	Placebo	26	-0.5	5.0	26	-0.5	12.6	26	-4.0	-21.9
	KALYDECO	24	4.5	(1.1, 8.8)	24	12.2	(5.0, 20.3)	23	-25.9	(-26.5, -17.3)
Subgroup by Poly-T Status †										
5T	Placebo	24	0.7	5.3	24	-0.6	15.3	24	-4.6	-24.2
	KALYDECO	14	6.0	(1.3, 9.3)	14	14.7	(7.7, 23.0)	13	-28.7	(-30.2, -18.2)
7T	Placebo	5	-0.9	0.2	5	-6.0	5.2	5	3.9	-24.1
	KALYDECO	11	-0.7	(-8.1, 8.5)	11	-0.7	(-13.0, 23.4)	10	-20.2	(-33.9, -14.3)
Subgroup by Baseline FEV_1 % Predicted										
<70%	Placebo	15	0.4	4.0	15	3.0	11.4	15	-3.8	-25.5
	KALYDECO	13	4.5	(-2.1, 10.1)	13	14.4	(1.2, 21.6)	12	-29.3	(-31.8, -19.3)
70-90%	Placebo	14	0.2	2.6	13	-3.6	8.8	14	-3.1	-20.0
	KALYDECO	14	2.8	(-2.3, 7.5)	14	5.2	(-2.6, 20.2)	14	-23.0	(-26.9, -12.9)
>90%	Placebo	6	2.2	-4.3	6	-2.5	-0.7	6	1.0	-26.8
	KALYDECO	7	-2.1	(-9.9, 1.3)	6	-3.2	(-10.4, 9.0)	6	-25.9	(-39.5, -14.1)

* MMRM analysis with fixed effects for treatment, age, week, baseline value, treatment by week, and subject as a random effect
† (n=54) Poly-T status confirmed by genotyping

14.4 Trial in Patients with CF Heterozygous for the *F508del* Mutation and a Second Mutation Predicted to be Responsive to ivacaftor

The efficacy and safety of KALYDECO and an ivacaftor-containing combination product in 246 patients with CF was evaluated in a randomized, double−blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover design clinical trial (Trial 7). Mutations predicted to be responsive to ivacaftor were selected for the study based on the clinical phenotype (pancreatic sufficiency), biomarker data (sweat chloride), and *in vitro* responsiveness to ivacaftor.

Eligible patients were heterozygous for the *F508del* mutation with a second mutation predicted to be responsive to ivacaftor. Of the 244 patients included in the efficacy analysis, who were randomized and dosed, 146 patients had a splice mutation and 98 patients had a missense mutation, as the second allele. 156 patients received KALYDECO and 161 patients received placebo. Patients were aged 12 years and older (mean age 35 years [range 12-72]) and had a percent predicted FEV_1 at screening between 40-90 [mean $ppFEV_1$ at study baseline 62 (range: 35 to 94)]. Patients with evidence of colonization with organisms associated with a more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*) and those with abnormal liver function at screening were excluded. Abnormal liver function was defined as 2 or more liver function tests (ALT, AST, ALP, GGT) ≥3 times the upper limit of normal or total bilirubin ≥2 times the upper limit of normal, or a single increase in ALT/AST ≥5 times the upper limit of normal.

The primary efficacy endpoint was the mean absolute change from study baseline in percent predicted FEV_1 averaged at Weeks 4 and 8 of treatment. The key secondary efficacy endpoint was absolute change in CFQ-R respiratory domain score from study baseline averaged at Weeks 4 and 8 of treatment. For the overall population, treatment with KALYDECO compared to placebo resulted in significant improvement in $ppFEV_1$ [4.7 percent points from study baseline to average of Week 4 and Week 8 (P<0.0001)] and CFQ-R respiratory domain score [9.7 points from study baseline to average of Week 4 and Week 8 (P<0.0001)]. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (Table 8).

Table 8: Effect of KALYDECO for Efficacy Variables

Mutation (n)	**Absolute Change in percent predicted FEV_1 *†**	**Absolute Change in CFQ-R Respiratory Domain Score (Points) *§**	**Absolute Change in Sweat Chloride (mmol/L) *§**
Splice mutations (n=94 for IVA and n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for KALYDECO vs. placebo-treated patients:			
	5.4 (4.1, 6.8)	8.5 (5.3, 11.7)	-2.4 (-5.0, 0.3)
By individual splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for KALYDECO-treated patients			
2789+5G→A (28)	5.1 (-7.1, 17.0)	8.6 (-5.6, 27.8)	0.4 (-7.5, 8.8)
3272-26A→G (23)	3.5 (-9.1, 16.0)	8.0 (-11.1, 27.8)	-2.3 (-25.0, 11.8)
3849+10kBc→T (40)	5.1 (-6.8, 16.2)	7.5 (-30.6, 55.6)	-4.6 (-80.5, 23.0)
711+3A→G (2)	9.2 (8.9, 9.6)	-8.3 (-13.9, -2.8)	-9.9 (-13.5, -6.3)
E831X (1)	7.1 (7.1, 7.1)	0.0 (0.0, 0.0)	-7.8 (-7.8, -7.8)
Missense mutations (n=62 for IVA and n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for KALYDECO vs. placebo-treated patients:			
	3.6 (1.9, 5.2)	11.5 (7.5, 15.4)	-7.8 (-11.2, -4.5)
By individual missense mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for KALYDECO-treated patients			
D579G (2)	13.3 (12.4, 14.1)	15.3 (-2.8, 33.3)	-30.8 (-36.0, -25.5)

Table 8: Effect of KALYDECO for Efficacy Variables			
Mutation (n)	**Absolute Change in percent predicted FEV_1 *†**	**Absolute Change in CFQ-R Respiratory Domain Score (Points) *§**	**Absolute Change in Sweat Chloride (mmol/L) *§**
D1152H (15)	2.4 (-5.0, 10.2)	13.7 (-16.7, 50.0)	-4.8 (-22.0, 3.0)
A455E (14)	3.7 (-6.6, 19.7)	6.8 (-13.9, 33.3)	7.5 (-16.8, 16.0)
L206W (2)	4.2 (2.5, 5.9)	12.5 (-5.6, 30.6)	3.9 (-8.3, 16.0)
P67L (12)	4.3 (-2.5, 25.7)	10.8 (-12.5, 36.1)	-10.5 (-34.8, 9.8)
R1070W (1)	2.9 (2.9, 2.9)	44.4 (44.4, 44.4)	0.3 (0.3, 0.3)
R117C (1)	3.5 (3.5, 3.5)	22.2 (22.2, 22.2)	-36.0 (-36.0, -36.0)
R347H (3)	2.5 (-0.6, 6.9)	6.5 (5.6, 8.3)	-19.2 (-25.8, -7.0)
R352Q (2)	4.4 (3.5, 5.3)	9.7 (8.3, 11.1)	-21.9 (-45.5, 1.8)
S945L (9)	8.8 (-0.2, 20.5)	10.6 (-25.0, 27.8)	-30.8 (-50.8, -17.3)
S977F (1)	4.3 (4.3, 4.3)	-2.8 (-2.8, -2.8)	-19.5 (-19.5, -19.5)

* Average of Week 4 and 8 values
† Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis.
§ Absolute change in CFQ-R respiratory domain score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.

In an analysis of BMI at Week 8, an exploratory end-point, patients treated with KALYDECO had a mean improvement of 0.28 kg/m^2 [95% CI (0.14, 0.43)], 0.24 kg/m^2 [95% CI (0.06, 0.43)], and 0.35 kg/m^2 [95% CI (0.12, 0.58)] versus placebo for the overall, splice, and missense mutation populations of patients, respectively.

14.5 Trial in Patients Homozygous for the *F508del* Mutation in the *CFTR* Gene

Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who had FEV_1 ≥40% predicted. Patients were randomized 4:1 to receive KALYDECO 150 mg (n=112) every 12 hours or placebo (n=28) in addition to their prescribed CF therapies. The mean age of patients enrolled was 23 years and the mean baseline FEV_1 was 79% predicted (range 40% to 129%). As in Trials 1 and 2, patients who had persistent *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded. The use of inhaled hypertonic saline was not permitted.

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV_1. The treatment difference from placebo for the mean absolute change in percent predicted FEV_1 through Week 16 in patients with CF homozygous for the *F508del* mutation in the *CFTR* gene was 1.72 percentage points (1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively) and did not reach statistical significance (Table 9).

Other efficacy variables that were analyzed included absolute change in sweat chloride from baseline through Week 16, change in cystic fibrosis respiratory symptoms through Week 16 as assessed by the CFQ-R respiratory domain score (Table 9), change in weight through Week 16, and rate of pulmonary exacerbation. The overall treatment difference for change from baseline in weight through Week 16 was -0.16 kg (95% CI -1.06, 0.74); the rate ratio for pulmonary exacerbation was 0.677 (95% CI 0.33, 1.37).

Table 9: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) Through 16 Weeks

		Absolute Change through Week 16 *- Full Analysis Set								
		% Predicted FEV_1 (Percentage Points)			**CFQ-R Respiratory Domain Score (Points)**			**Sweat Chloride (mmol/L)**		
Subgroup Parameter	Study Drug	n	Mean	Treatment Difference (95% CI)	n	Mean	Treatment Difference (95% CI)	n	Mean	Treatment Difference (95% CI)
F508del homozygous										
	Placebo	28	-0.2	1.72	28	-1.44	1.3	28	0.13	-2.9
	KALYDECO	111	1.5	(-0.6, 4.1)	111	-0.12	(-2.9, 5.6)	109	-2.74	(-5.6, -0.2)

* MMRM analysis with fixed effects for treatment, age week, baseline value, treatment by week, and subject as a random effect

16 HOW SUPPLIED/STORAGE AND HANDLING

KALYDECO (ivacaftor) tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with the characters "V 150" on one side and plain on the other, and is packaged as follows:

56-count carton (contains 4 individual blister cards of 14 tablets per card)	**NDC** 51167-200-01
60-count bottle	**NDC** 51167-200-02

KALYDECO (ivacaftor) oral granules are supplied as small, white to off-white granules and enclosed in unit-dose packets as follows:

56-count carton (contains 56 unit-dose packets of 25 mg ivacaftor per packet)	**NDC** 51167-600-01
56-count carton (contains 56 unit-dose packets of 50 mg ivacaftor per packet)	**NDC** 51167-300-01
56-count carton (contains 56 unit-dose packets of 75 mg ivacaftor per packet)	**NDC** 51167-400-01

Store at 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Transaminase (ALT or AST) Elevations and Monitoring
Inform patients that elevation in liver tests have occurred in patients treated with KALYDECO. Liver function tests will be performed prior to initiating KALYDECO, every 3 months during the first year of treatment and annually thereafter. More frequent monitoring of liver function tests should be considered in patients with a history of transaminase elevations *[see Warnings and Precautions (5.1)]*.

Drug Interactions with CYP3A Inducers and Inhibitors
Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of KALYDECO with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended, as they may reduce the therapeutic effectiveness of KALYDECO. Reduction of the dose of KALYDECO to one tablet or one packet of granules twice a week is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Dose reduction to one tablet or one packet of granules once daily is recommended when co-administered with moderate CYP3A inhibitors, such as fluconazole. Food containing grapefruit or Seville oranges should be avoided *[see Drug Interactions (7.1, 7.2) and Clinical Pharmacology (12.3)]*.

Use in Patients with Hepatic Impairment
Inquire and/or assess whether patients have liver impairment. Reduce the dose of KALYDECO in patients with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) to one tablet or one packet of granules once daily. KALYDECO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C, score 10-15); however, exposure is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, KALYDECO should be used with caution in patients with severe hepatic impairment at a dose of one tablet or one packet of granules given once daily or less frequently. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A, score 5-6) *[see Use in Specific Populations (8.6)]*.

Administration
KALYDECO® (ivacaftor) tablets 150 mg
Inform patients that KALYDECO tablet is best absorbed by the body when taken with food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc.

KALYDECO® (ivacaftor) oral granules 25 mg, 50 mg or 75 mg
Inform patients and caregivers that KALYDECO oral granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed to ensure delivery of the entire dose. Food or liquid should be at or below room temperature. Once mixed, the product has been shown to be stable for one hour, and therefore should be consumed during this period. Some examples of appropriate soft foods or liquids may include puréed fruits or vegetables, yogurt, applesauce, water, breast milk, infant formula, milk, or juice.

Inform patients and caregivers that KALYDECO is best absorbed by the body when taken with food that contains fat; therefore, KALYDECO oral granules should be taken just before or just after consuming food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc.

Patients should be informed about what to do in the event they miss a dose of KALYDECO:
- In case a dose of KALYDECO is missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of KALYDECO with fat-containing food as soon as possible.
- If more than 6 hours have passed since KALYDECO is usually taken, the missed dose should NOT be taken and the patient should resume the usual dosing schedule.
- Patients should be advised to contact their healthcare provider if they have questions.

Cataracts
Inform patients that abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. Baseline and follow-up ophthalmological examinations should be performed in pediatric patients initiating KALYDECO treatment *[see Warnings and Precautions (5.3)]*.

VERTEX

Manufactured for
Vertex Pharmaceuticals Incorporated
Boston, MA 02210

Revised XX 2019

Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION

KALYDECO (kuh-LYE-deh-koh) (ivacaftor) Film-Coated Tablets and Oral Granules

Read this Patient Information before you start taking KALYDECO and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is KALYDECO?

KALYDECO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have at least one mutation in their CF gene that is responsive to KALYDECO.

Talk to your doctor to learn if you have an indicated CF gene mutation.

It is not known if KALYDECO is safe and effective in children under 6 months of age.

Who should not take KALYDECO?

Do not take KALYDECO if you take certain medicines or herbal supplements such as:

- the antibiotics rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medications such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, Equetro®) or phenytoin (Dilantin®, Phenytek®)
- St. John's wort

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking KALYDECO?

Before you take KALYDECO, tell your doctor if you:

- have liver or kidney problems
- drink grapefruit juice, or eat grapefruit or Seville oranges
- are pregnant or plan to become pregnant. It is not known if KALYDECO will harm your unborn baby. You and your doctor should decide if you will take KALYDECO while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if KALYDECO passes into your breast milk. You and your doctor should decide if you will take KALYDECO while you are breastfeeding.

KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements, as the dose of KALYDECO may need to be adjusted when taken with certain medications.

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Especially tell your doctor if you take:

- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), voriconazole (e.g., Vfend®), or fluconazole (e.g., Diflucan®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take KALYDECO?

- Take KALYDECO exactly as your doctor tells you to take it.
- Take your doses of KALYDECO 12 hours apart.
- If you miss a dose of KALYDECO and it is **within 6 hours** of when you usually take it, take your dose of KALYDECO as prescribed with fat-containing food as soon as possible.
- If you miss a dose of KALYDECO and it is **more than 6 hours** after the time you usually take it, **skip that dose only** and take the next dose when you usually take it. Do **not** take 2 doses at the same time to make up for your missed dose.

KALYDECO Tablets (ages 6 years and older):

- Always take KALYDECO tablets with food that contains fat. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, and whole-milk dairy products such as whole milk, cheese, and yogurt.
- Each KALYDECO box contains 4 individual blister cards.
- Each blister card contains 14 pills—7 morning doses and 7 evening doses.
- In the morning, unpeel the paper backing from a blister card to remove 1 KALYDECO tablet and take it with food that contains fat.
- In the evening, 12 hours later, open another blister card to remove 1 KALYDECO tablet and take it with food that contains fat.
- You may cut along the dotted line to separate your doses from the blister card.

KALYDECO Oral Granules (ages 6 months to under 6 years old):

- Hold the packet with cut line on top.
- Shake the packet gently to settle the KALYDECO granules.
- Tear or cut packet open along cut line.
- Carefully pour all of the KALYDECO granules in the packet into 1 teaspoon of soft food or liquid. Food or liquid should be at or below room temperature. Some examples of soft foods or liquids include puréed fruits or vegetables, yogurt, applesauce, water, breast milk, infant formula, milk, or juice.
- Mix the KALYDECO granules with food or liquid.
- After mixing, give KALYDECO within 1 hour. Make sure all medicine is taken.
- Give a child fat-containing food just before or just after the KALYDECO granules dose. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, and whole-milk dairy products such as whole milk, cheese, and yogurt.

What should I avoid while taking KALYDECO?

- KALYDECO can cause dizziness in some people who take it. Do not drive a car, use machinery or do anything that needs you to be alert until you know how KALYDECO affects you.
- You should avoid food containing grapefruit or Seville oranges while you are taking KALYDECO.

What are the possible side effects of KALYDECO?

KALYDECO can cause serious side effects.

High liver enzymes in the blood have been reported in patients receiving KALYDECO. Your doctor will do blood tests to check your liver:

- before you start KALYDECO
- every 3 months during your first year of taking KALYDECO
- every year while you are taking KALYDECO

For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often.

Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO.

Your doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts.

The most common side effects of KALYDECO include:

- headache
- upper respiratory tract infection (common cold), including:
    - sore throat
    - nasal or sinus congestion
    - runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- nausea
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KALYDECO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KALYDECO?

- Store KALYDECO at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Do not use KALYDECO after the expiration date on the package.

Keep KALYDECO and all medicines out of the reach of children.

General information about the safe and effective use of KALYDECO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KALYDECO for a condition for which it was not prescribed. Do not give KALYDECO to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about KALYDECO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about KALYDECO that is written for health professionals.

For more information, go to www.kalydeco.com or call 1-877-752-5933.

What are the ingredients in KALYDECO?

Active ingredient: ivacaftor
Inactive ingredients:
KALYDECO Tablets are light blue, film-coated, capsule-shaped tablets for oral administration and contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

The tablet film coat contains: carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide.

The printing ink contains: ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

KALYDECO Oral Granules are white to off-white granules for oral administration (sweetened but unflavored) and contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

VERTEX
Manufactured for:
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Approved XX 2019