KALYDECO® (ivacaftor):

Treating the underlying cause of cystic fibrosis (CF) in patients 1 month and older[1]*

An overview of clinical trial data in patients with CF age 1 month to less than 24 months[1]*

*Use of KALYDECO in patients age 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated.[1]

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

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

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

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- 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

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Overview of KALYDECO in patients with CF age 1 month and older[a]

PATIENTS AGE 1 MONTH TO LESS THAN 24 MONTHS

TRIAL 8 (ARRIVAL)

Phase 3, 24-week, open-label, single-arm study with multiple cohorts[1-3]:

1 month to less than 4 months (n=7)
Genotype eligible: any ivacaftor-responsive mutation

4 months to less than 6 months (n=6)
6 months to less than 12 months (n=11)
12 months to less than 24 months (n=19)
Genotype eligible: 1 or more gating mutation or *R117H*

PATIENTS AGE 2 YEARS THROUGH 5 YEARS

TRIAL 6 (KIWI)

Phase 3, 24-week, open-label, single-arm study (N=34)[4]
Genotype eligible: gating mutation on at least one allele

PATIENTS AGE 6 YEARS AND OLDER

TRIAL 2 (ENVISION)

Phase 3, 48-week, randomized, double-blind, placebo-controlled study, age 6 years to less than 12 years (N=52)[5]
Genotype eligible: 1 or more *G551D* mutation

TRIAL 4 (KONNECTION)

Phase 3, randomized, double-blind, placebo-controlled, 2-part crossover study (N=39)[6]
Genotype eligible: non-*G551D* gating mutation on at least one allele

TRIAL 5 (KONDUCT)

Phase 3, 24-week, randomized, double-blind, placebo-controlled, parallel-group study (N=69)[7]
Genotype eligible: 1 or more *R117H* mutation

PATIENTS AGE 12 YEARS AND OLDER

TRIAL 1 (STRIVE)

Phase 3, 48-week, randomized, double-blind, placebo-controlled study (N=161)[8]
Genotype eligible: 1 or more *G551D* mutation

TRIAL 3 (DISCOVER)

Phase 2, 16-week, randomized, double-blind, placebo-controlled, parallel-group study (N=140)[1,9]
Genotype eligible: homozygous for the *F508del* mutation

TRIAL 7 (EXPAND)

Phase 3, 8-week, randomized, double-blind, placebo-controlled crossover study (N=246)[10]
Genotype eligible: heterozygous for the *F508del-CFTR* mutations and a second mutation that results in residual CFTR function

[a]Use of KALYDECO in patients age 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated.[1]

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CFTR mutations responsive to KALYDECO

LIST OF *CFTR* GENE MUTATIONS THAT PRODUCE CFTR PROTEIN AND ARE RESPONSIVE TO KALYDECO[1]

A1067T	*E56K*	*G178E*	*I175V*	*Q237E*	*R347H**	*S549N**	*Y1014C*
A120T	*E822K*	*G178R**	*I807M*	*Q237H*	*R347L*	*S549R**	*Y1032C*
A234D	*E831X**	*G194R*	*K1060T*	*Q359R*	*R352Q**	*S589N*	*2789+5G→A**
A349V	*F1052V*	*G314E*	*L1480P*	*R1070Q*	*R553Q*	*S737F*	*3272-26A→G**
*A455E**	*F1074L*	*G551D**	*L206W**	*R1070W**	*R668C*	*S945L**	*3849+10kbC→T**
D110E	*F311del*	*G551S**	*L320V*	*R1162L*	*R74W*	*S977F**	*711+3A→G**
D110H	*F311L*	*G576A*	*L967S*	*R117C**	*R75Q*	*T1053I*	
*D1152H**	*F508C*	*G970D*	*L997F*	*R117G*	*R792G*	*T338I*	
D1270N	*F508C;S1251N*[†]	*H1375P*	*M152V*	*R117H**	*R933G*	*V1293G*	
D192G	*G1069R*	*H939R*	*M952I*	*R117L*	*S1159F*	*V232D*	
*D579G**	*G1244E**	*I1027T*	*M952T*	*R117P*	*S1159P*	*V562I*	
D924N	*G1249R*	*I1139V*	*P67L**	*R1283M*	*S1251N**	*V754M*	
E193K	*G1349D**	*I148T*	*Q1291R*	*R170H*	*S1255P**	*W1282R*	

*Clinical data exist for these mutations.[1]
[†]Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.[1]
CFTR, cystic fibrosis transmembrane conductance regulator.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Transaminase (ALT or AST) Elevations (cont'd)

- 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

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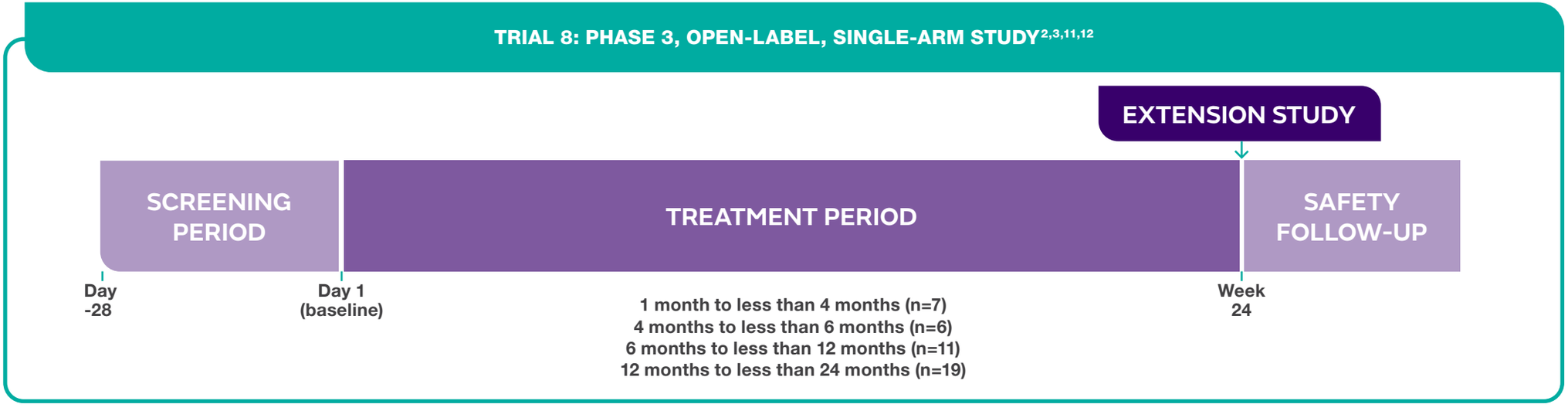
Trial 8 (ARRIVAL): Patients with CF age 1 month to less than 24 months (N=43)

KALYDECO was studied in patients as young as 1 month[a]



Primary endpoint[2,3,13]

- Safety, assessed by adverse events (AEs) and clinical laboratory assessments

Select secondary endpoint[2,3,13]

- Absolute change from baseline in sweat chloride concentration through week 24 in the 1 to <4 months cohort. Absolute change from baseline in sweat chloride concentration at week 24 in the 4 to <6 months, 6 to <12 months, and 12 to <24 months cohorts

Key inclusion criteria[b]

- Patients with a gating mutation or *R117H* mutation were eligible for the 1 to less than 4 months[c], 4 to less than 6 months, 6 to less than 12 months, and 12 to less than 24 months cohorts of the study cited above[11,12,16d]
- Patients with 1 or more ivacaftor-responsive mutations were eligible for the cohort of patients age 1 to less than 4 months[1d]
- Confirmed CF diagnosis[12]
- Body weight ≥3 kg at screening[1]

[a]Use of KALYDECO in patients age 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated.[1]
[b]Selected exclusion criteria included an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1; abnormal liver function at screening or any prior history of clinically relevant elevated >2x upper limit of normal (ULN) aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin (excluding newborn hyperbilirubinemia); history of solid organ or hematological transplantation.[12]
[c]Infants with an R117H genotype had to have either the 5T variant or a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis at screening.[11]
[d]Included gestational age ≥38 weeks.[12,13]

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Trial 8 (ARRIVAL): Patients with CF age 1 month to less than 24 months (N=43)

KALYDECO was studied in patients as young as 1 month[a] (cont'd)

INTERRUPTIONS, DISCONTINUATIONS, AND SERIOUS ADVERSE EVENTS (AEs)

PRIMARY ENDPOINT

1-<4 months (n=7)[1,11]

- 1 patient discontinued treatment due to an AE of elevated transaminase noted to be concurrent with a gastrointestinal illness and other subsequent viral illnesses
  - The AE was assessed by the investigator as unlikely to be related to ivacaftor

4-<6 months (n=6)[14]

- 1 patient experienced a serious AE (bronchiolitis) considered unlikely related to trial drug
- 0 patients interrupted or discontinued treatment due to AEs

6-<12 months (n=11)[15]

- 3 patients experienced serious AEs (1 with viral respiratory tract infection, 1 with viral rash, and 1 with cough)
- 1 patient interrupted treatment due to eczema
- 0 patients discontinued treatment due to AEs

12-<24 months (n=19)[3]

- 1 patient withdrew due to difficulty with blood draws
- 2 patients experienced serious AEs (1 with constipation, DIOS, and eczema herpeticum and 1 with persistent cough)
- The serious AE of constipation was considered possibly related to KALYDECO treatment by the investigator
- The patient with persistent cough required hospitalization for 2 weeks and treatment with intravenous antibiotics

The safety profile of patients in this trial was similar to that observed in patients age 2 years and older.[1]
Please click here to see adverse events and additional safety information.

[a]Use of KALYDECO in patients age 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated.[1]
AE, adverse event; DIOS, distal intestinal obstruction syndrome.

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Trial 8 (ARRIVAL): Patients with CF age 1 month to less than 24 months (N=43)

KALYDECO was studied in patients as young as 1 month[a] (cont'd)

Transaminase elevations

MAXIMUM ELEVATIONS OF TRANSAMINASE ELEVATIONS IN FOUR TRIAL 8 COHORTS[1] — **PRIMARY ENDPOINT**

ELEVATED ALT OR AST	1 TO LESS THAN 4 MONTHS, n/N (%)	4 TO LESS THAN 6 MONTHS, n/N (%)	6 TO LESS THAN 12 MONTHS, n/N (%)	12 TO LESS THAN 24 MONTHS, n/N (%)
>3-≤5x ULN	0/7 (0.0)	0/6 (0.0)	1/11 (9.1)	5/18 (27.8)
>5-≤8x ULN	0/7 (0.0)	0/6 (0.0)	0/11 (0.0)	2/18 (11.1)
>8x ULN	1/7 (14.3)	0/6 (0.0)	0/11 (0.0)	2/18 (11.1)

TREATMENT DISCONTINUATIONS AND INTERRUPTIONS DUE TO TRANSAMINASE ELEVATIONS — **PRIMARY ENDPOINT**

1-<4 months (n=7)[1,11]
- 1 patient discontinued treatment due to an AE of elevated transaminase noted to be concurrent with a gastrointestinal illness and other subsequent viral illnesses

4-<6 months (n=6)[16]
- 0 patients interrupted or discontinued treatment due to transaminase elevations

6-<12 months (n=11)[16]
- 0 patients interrupted or discontinued treatment due to transaminase elevations

12-<24 months (n=19)[3]
- 0 patients discontinued treatment due to transaminase elevations
  - 2 patients interrupted treatment due to transaminase elevations (>8x ULN). Both patients resumed treatment with no further elevations in Trial 8

[a]Use of KALYDECO in patients age 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated.[1]

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Trial 8 (ARRIVAL): Patients with CF age 1 month to less than 24 months (N=43)

KALYDECO pharmacodynamic results

Reductions in sweat chloride concentrations were observed across all cohorts

MEAN ABSOLUTE CHANGE FROM BASELINE IN SWEAT CHLORIDE CONCENTRATION[1] **SECONDARY ENDPOINT**

Patients age 1 to <4 months (n=5)

-40.3 mmol/L
THROUGH WEEK 24
(95% CI -76.6, -4.1)

Patients age 4 to <6 months (n=3)

-50.0 mmol/L
AT WEEK 24
(95% CI: -93.1, -6.9)

Patients age 6 to <12 months (n=6)

-58.6 mmol/L[a]
AT WEEK 24
(95% CI: -75.9, -41.3)

Patients age 12 to <24 months (n=10)

-73.5 mmol/L
AT WEEK 24
(95% CI: -86.0, -61.0)

[a]Calculated from children with data available at both baseline and Week 24.[2]
CI, confidence interval.

There was no direct correlation between decrease in sweat chloride levels and improvement in lung function (FEV_1)[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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Trial 1: Patients with CF age 12 years and older (N=161)
Trial 2: Patients with CF age 6 to less than 12 years old (N=52)

KALYDECO was evaluated in patients age 6 years and older with CF

STUDIES OF KALYDECO IN PATIENTS AGE 6 YEARS AND OLDER[1]

TRIALS 1 AND 2[a]
Phase 3, randomized, double-blind, placebo-controlled studies

48-WEEK TREATMENT

KALYDECO
150 mg q12h (n=109)

PLACEBO
(n=104)

[a]Trial 1 evaluated 161 patients with CF who were age 12 years and older who had the *G551D* mutation. Trial 2 evaluated 52 patients with CF who were age 6 to 11 years who had the *G551D* mutation. Eligible patients were rolled over into an open-label Extension Study.[1]

- All patients in Trials 1 and 2 remained on currently prescribed CF therapies[1]

Primary endpoint[1]

- 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 (Trials 1 and 2)

Selected secondary endpoints[1b]

- Absolute change from baseline in sweat chloride
- Absolute change from baseline in weight
- Improvement from baseline in CFQ-R respiratory domain score

Key inclusion criteria[1]

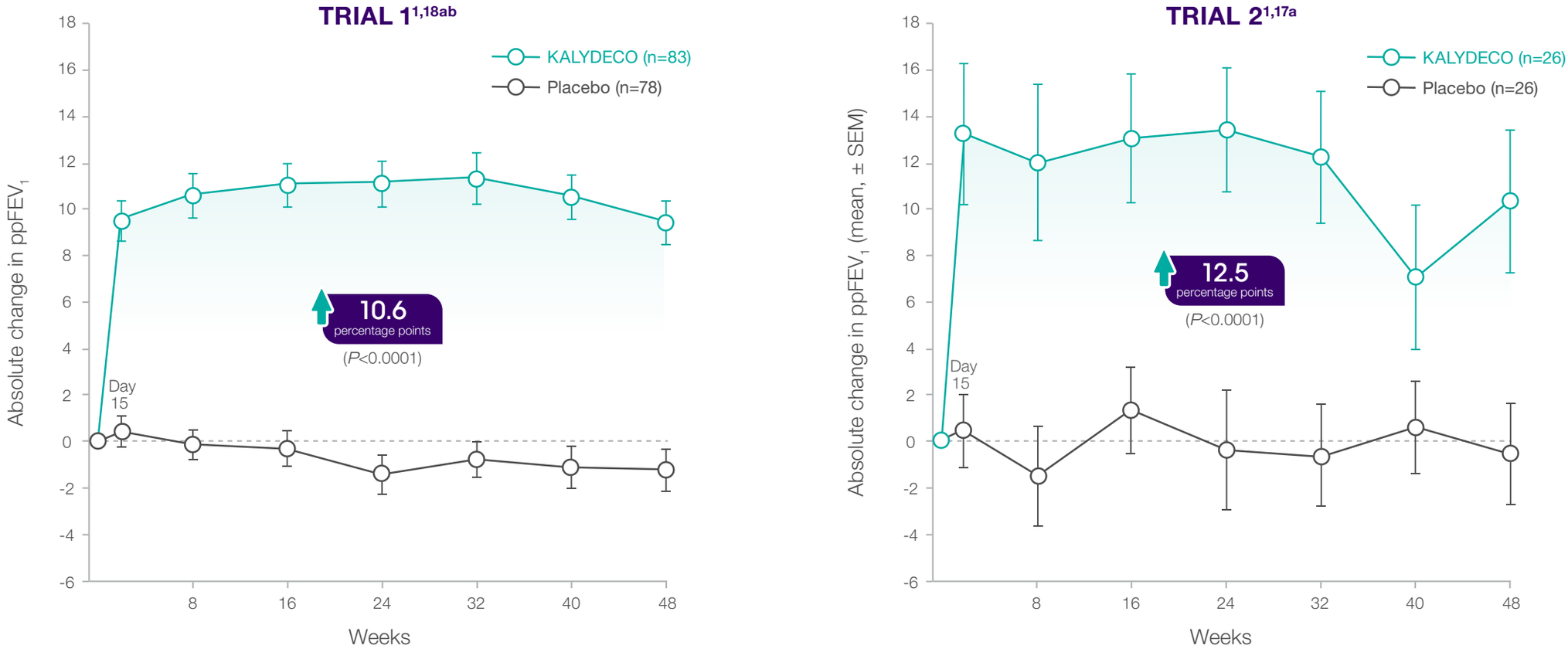
- $ppFEV_1$ between 40 and 90 at screening (Trial 1)
- $ppFEV_1$ between 40 and 105 at screening (Trial 2)

Key exclusion criteria[1]

- Persistent *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening
- Abnormal liver function defined as ≥3 liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3x ULN

[b]For Trials 1 and 2, selected secondary endpoints were assessed through/at Week 24 and Week 48.[1]
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CFQ-R, Cystic Fibrosis Questionnaire-Revised; GGT, gamma-glutamyl transferase; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; ULN, upper limit of normal.

Treatment with KALYDECO resulted in a significant improvement in FEV_1[1]



[a]Primary endpoint was assessed at the 24-week time point.[1]
[b]The 95% confidence intervals are indicated by the I bars.
SEM, standard error of mean.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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Overall KALYDECO safety profile established in clinical trials

The overall safety profile for KALYDECO is based on Trials 1, 2, and 3[1ab]

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

Pooled safety data from Trials 1, 2, and 3[1ab]

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

- Serious adverse events that occurred more frequently in patients treated with KALYDECO included: **ABDOMINAL PAIN** | **INCREASED HEPATIC ENZYMES** | **HYPOGLYCEMIA**

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

Most common adverse events in Trials 1 and 2[1a]

MOST COMMON ADVERSE EVENTS (≥8%) IN PATIENTS WITH A *G551D* MUTATION TREATED WITH KALYDECO AND HIGHER THAN PLACEBO[1]

ADVERSE REACTION (PREFERRED TERM)	KALYDECO (n=109), n (%)	PLACEBO (n=104), n (%)
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

- The safety profile for the patients with CF enrolled in the other clinical trials was similar to that observed in the 48-week, placebo-controlled Trials 1 and 2[1a]

[a]Trials 1 and 2 were 48-week, randomized, double-blind, placebo-controlled trials in 213 patients with a *G551D* mutation. Trial 1 patients were age 12 years and older; Trial 2 patients were age 6 to 11 years.[1]

[b]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. KALYDECO is not indicated in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.[1]

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Overall KALYDECO safety profile established in clinical trials (cont'd)

Transaminase elevations in patients age 6 years and older[1ab]

- In Trials 1, 2 and 3, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3x ULN was 2%, 2%, and 6% in patients treated with KALYDECO and 2%, 2%, and 8% in patients given placebo, respectively
- The proportion of patients who permanently discontinued treatment for elevated transaminases, all >8x ULN, was 0.5% for patients treated with KALYDECO and 2% for patients given placebo
- 2 patients treated with KALYDECO were reported to have serious adverse events of elevated liver transaminases compared with none on placebo
- Transaminase elevations were more common in patients with a history of transaminase elevations

Transaminase elevations in patients age 1 month to less than 6 years[1,11cd]

- In Trial 6, the incidence of patients experiencing transaminase elevations (ALT or AST) >3x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8x ULN that returned to baseline levels following interruption of KALYDECO dosing
  - Transaminase elevations were more common in patients who had abnormal transaminases at baseline
  - One patient permanently discontinued treatment with KALYDECO due to transaminase elevations
- In Trial 8, 1 patient (14.3%) from the cohort of patients age 1 to less than 4 months (n=7) had maximum ALT >8x ULN and maximum AST of >3 to ≤5x ULN; the subject discontinued ivacaftor treatment. The event was considered unlikely to be related to KALYDECO and was noted to be concurrent with a gastrointestinal illness and other subsequent viral illnesses experienced by the patient. In the cohort of patients age 4 to less than 6 months (n=6), no patients experienced transaminase elevations. In the cohort of patients age 6 to less than 12 months (n=11), 1 patient (9.1%) had elevated ALT of >3 to ≤5x ULN. The incidence of patients experiencing ALT or AST >3, >5, and >8x ULN in the cohort of patients age 12 to less than 24 months (n=19) was 27.8% (5/18), 11.1% (2/18) and 11.1% (2/18), respectively

Transaminase elevation monitoring[1]

- 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

[a]Trials 1 and 2 were 48-week, randomized, double-blind, placebo-controlled trials in 213 patients with a *G551D* mutation. Trial 1 patients were age 12 years and older; Trial 2 patients were age 6 to 11 years.[1]

[b]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. KALYDECO is not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.[1]

[c]Trial 6 was a 24-week, open-label trial in 34 patients. Patients were eligible if they had a *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R* mutation. Of the 34 patients enrolled, 32 had a *G551D* mutation and 2 had a *S549N* mutation. Trial 6 patients were age 2 to less than 6 years.[1]

[d]Trial 8 was a 24-week, open-label trial in a cohort of 19 patients age 12 months to less than 24 months, a cohort of 11 patients age 6 months to less than 12 months, and a cohort of 6 patients age 4 months to less than 6 months who could have a *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *R117H* (eligible for this study only in the United States), *S1251N*, *S1255P*, *S549N*, or *S549R* mutation, as well as a cohort of 7 patients age 1 month to less than 4 months who had ivacaftor-responsive mutations.[1]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

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Recommended dosing for KALYDECO[1]

FOR PATIENTS AGE 1 TO LESS THAN 2 MONTHS

- ≥3 kg[a]: One 5.8-mg granules packet every 12 hours

FOR PATIENTS AGE 2 TO LESS THAN 4 MONTHS

- ≥3 kg[a]: One 13.4-mg granules packet every 12 hours

FOR PATIENTS AGE 4 TO LESS THAN 6 MONTHS

- ≥5 kg[b]: One 25-mg granules packet every 12 hours

Each dose of KALYDECO should be administered just before or just after fat-containing food

FOR PATIENTS AGE 6 MONTHS TO LESS THAN 6 YEARS

- 5 kg to <7 kg[b]: One 25-mg granules packet every 12 hours

- 7 kg to <14 kg[c]: One 50-mg granules packet every 12 hours

- ≥14 kg[d]: One 75-mg granules packet every 12 hours

FOR PATIENTS AGE 6 YEARS AND OLDER

- One 150-mg tablet every 12 hours

Granules and tablets pictured above are not actual size.

Patients should continue taking all of their prescribed CF therapies with KALYDECO[1]

- The safety and efficacy of KALYDECO for patients age less than 1 month have not been established. The use of KALYDECO in children less than 1 month is not recommended[1]
- Use of KALYDECO in patients age 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated[1]
- KALYDECO is not recommended for use in children age 1 month to less than 6 months with any level of hepatic impairment and/or taking concomitant moderate or strong CYP3A inhibitors[1]

[a]≥3 kg ≈ ≥7 lb.
[b]5 kg to <7 kg ≈ 11 lb to <15 lb.
[c]7 kg to <14 kg ≈ 15 lb to <31 lb.
[d]≥14 kg ≈ ≥31 lb.

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

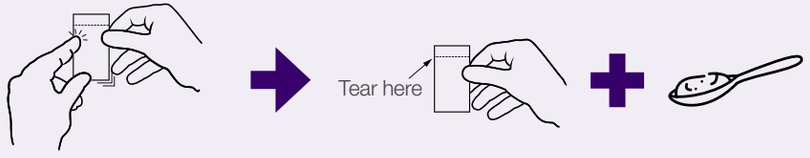
How to administer KALYDECO oral granules: 3 steps

1 PREPARATION[1]

- Caregiver should hold the packet with the cut line on top, shake the packet gently to settle the granules, and tear or cut the packet open along the cut line
- Caregiver should mix all granules into 1 teaspoon (5 mL) of soft food or liquid
- Food or liquid should be at or below room temperature

EXAMPLES OF SOFT FOODS AND LIQUIDS TO MIX WITH KALYDECO GRANULES FOR CHILDREN:

- Breast milk or infant formula
- Applesauce
- Water
- Puréed vegetables or fruits
- Milk or yogurt
- Juice



Note: Examples of soft foods or liquids include:

2 ADMINISTRATION[1]

- After mixing granules, caregiver should give the dose within 1 hour
- Caregiver should make sure the child finishes the dose completely

3 GIVE WITH FAT-CONTAINING FOOD[1]

- Food that contains fat must be taken just before or just after the oral granules dose

EXAMPLES OF FAT-CONTAINING FOODS FOR CHILDREN:

- Breast milk or infant formula
- Yogurt[a]
- Cheese pizza[a]
- Cheese[a]
- Butter
- Eggs
- Whole milk
- Peanut butter

Avoid foods and drinks that contain grapefruit, as these may affect the amount of KALYDECO in the body.[1]

Keep your patients' age in mind when recommending fat-containing foods to caregivers.

[a]Be sure that cheeses and yogurts are made with whole milk.[1]

It is important that patients consume the entire oral granules mixture with each dose[1]

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Dosage adjustments for KALYDECO

KALYDECO DOSAGE ADJUSTMENTS[1]	
DOSAGE ADJUSTMENTS FOR PATIENTS AGE 1 TO LESS THAN 6 MONTHS	**DOSE AND ADMINISTRATION FREQUENCY**
HEPATIC IMPAIRMENT	
Any impairment	Use is not recommended
CYP3A INHIBITORS	
Co-administration with **strong** or **moderate** CYP3A inhibitors[ab]	Concomitant use is not recommended
DOSAGE ADJUSTMENTS FOR PATIENTS AGE ≥6 MONTHS	
HEPATIC IMPAIRMENT	
Severe impairment (Child-Pugh Class C)	Use with caution after weighing the risks and benefits of treatment. One dose once daily, or less frequently[c]
Moderate impairment (Child-Pugh Class B)	One dose once daily[c]
Mild impairment (Child-Pugh Class A)	No dose adjustment required
CYP3A INHIBITORS	
Co-administration with **strong** CYP3A inhibitors[a]	One dose twice a week[c]
Co-administration with **moderate** CYP3A inhibitors[b]	One dose once daily[c]

Missed dose of oral granules[1]

- If ≤6 hours have passed: Advise caregivers to administer the dose with fat-containing food
- If >6 hours have passed: Advise caregivers to skip administration of that dose and resume the normal schedule for the following dose. A double dose should NOT be taken to make up for the forgotten dose

[a]Use of KALYDECO with a strong CYP3A inhibitor significantly increased ivacaftor exposure. Examples include ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.[1]

[b]Use of KALYDECO with a moderate CYP3A inhibitor increased ivacaftor exposure. Examples include fluconazole and erythromycin. Avoid foods and drinks that contain grapefruit, as these may affect the amount of KALYDECO in the body.[1]

Use of KALYDECO with strong CYP3A inducers significantly decreases the exposure of ivacaftor. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St John's wort, is not recommended.[1]

[c]For patients age 6 years and older, one dose is one tablet. For patients age 1 month to less than 6 years, one dose is one weight-based packet of oral granules.[1]

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VERTEX

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