AUSTRALIAN PI – KALYDECO® (IVACAFTOR) GRANULES & FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Ivacaftor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets
KALYDECO (ivacaftor) film-coated tablets contain 150 mg of ivacaftor per tablet.

Excipient with known effect: lactose monohydrate.

Granules
KALYDECO (ivacaftor) granules contain 13.4 mg, 25 mg, 50 mg or 75 mg of ivacaftor per sachet.

Excipient with known effect: lactose monohydrate, sucralose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

KALYDECO (ivacaftor) film-coated tablets are light blue, capsule-shaped tablets (16.5 mm x 8.4 mm in modified caplet shape). Each tablet is printed with "V 150" in black ink on one side only.

KALYDECO (ivacaftor) granules are white to off-white, sweetened, unflavoured granules (approximately 2 mm in diameter) enclosed in unit dose sachets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients aged 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 5.1 PHARMACODYNAMIC PROPERTIES).

4.2 DOSE AND METHOD OF ADMINISTRATION

KALYDECO should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of an indicated mutation in at least one allele of the *CFTR* gene before starting treatment (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

In patients with *R117H* mutation, analysis of the poly-T variants should be performed. In asymptomatic patients with *R117H-7T* a sweat test should be conducted and a diagnosis of CF confirmed prior to starting treatment.

Adults, adolescents, and children aged 1 month and older should be dosed according to Table 1.

Table 1: Dosing recommendations for patients aged 1 month and older with at least one of the indicated mutations in at least one allele of the *CFTR* gene		
Age	**Weight**	**Dose**
1 month to less than 2 months*†	≥3 kg	One sachet of 13.4 mg granules every 24 hours
2 months to less than 4 months	≥3 kg	One sachet of 13.4 mg granules every 12 hours
4 months to less than 6 months†	≥5 kg	One sachet of 25 mg granules every 12 hours
6 months and older	≥5 kg to <7 kg	One sachet of 25 mg granules every 12 hours
	≥7 kg to <14 kg	One sachet of 50 mg granules every 12 hours
	≥14 kg to <25 kg	One sachet of 75 mg granules every 12 hours
	≥25 kg	One 150 mg tablet every 12 hours

*Ivacaftor is not recommended for use in children under 1 month of age.
†Use of ivacaftor in patients aged 1 to less than 6 months born at a gestational age <37 weeks has not been evaluated.

A fat-containing meal or snack should be consumed just before or just after dosing of KALYDECO. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. A serving size of foods appropriate for age from a typical CF diet should be given. Examples of meals that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, avocados, whole milk, breast milk, infant formula, full-fat yoghurt, or meats. Food containing grapefruit should be avoided during treatment with KALYDECO (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Tablets
For oral use. Patients should be instructed to swallow the tablets whole (i.e., patients should not chew, break or dissolve the tablet).

Granules
For oral use. The entire content of each sachet of granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. Food or liquid should be at room temperature or below. Each sachet is for single use only. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period. Some examples of soft foods or liquids include puréed fruits or vegetables, yoghurt, applesauce, water, milk, breast milk, infant formula, or juice.

Use in the elderly
The efficacy and safety of KALYDECO in patients aged 65 years or older have not been evaluated.

Use in renal impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using KALYDECO in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES)

Use in hepatic impairment

Patients aged 1 month to less than 4 months

Treatment with ivacaftor is not recommended in patients aged 1 month to less than 4 months with any level of hepatic impairment.

Patients aged 4 months to less than 6 months

Treatment with ivacaftor is not recommended in patients aged 4 months to less than 6 months with any level of hepatic impairment, unless the benefits outweigh the risks. In such cases, the recommended dose is one sachet of 25 mg granules once daily or less frequently (see Table 2). Dosing intervals should be modified according to clinical response and tolerability (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Patients aged 6 months and older

No dose adjustment is necessary for patients aged 6 months and older with mild hepatic impairment (Child-Pugh Class A). A reduced dose of KALYDECO is recommended for patients with moderate hepatic impairment (Child-Pugh Class B) (see Table 2).

There is no experience with the use of KALYDECO in patients aged 6 months and older with severe hepatic impairment (Child-Pugh Class C). The use of KALYDECO in these patients is therefore not recommended unless the benefits outweigh the risks. In such cases KALYDECO should be used with caution at a reduced dose (see Table 2). Dosing intervals should be modified according to clinical response and tolerability (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Table 2: Dose adjustment recommendations in patients with hepatic impairment

Age/Weight	**Mild (Child-Pugh Class A)**	**Moderate (Child-Pugh Class B)**	**Severe (Child-Pugh Class C)**
1 month to less than 4 months	Not recommended	Not recommended	Not recommended
4 months to less than 6 months, ≥5 kg	Not recommended unless the benefit outweighs the risk. Dose as follows in such cases: One sachet of ivacaftor 25 mg granules once daily or less frequently*	Not recommended unless the benefit outweighs the risk. Dose as follows in such cases: One sachet of ivacaftor 25 mg granules once daily or less frequently*	Not recommended unless the benefit outweighs the risk. Dose as follows in such cases: One sachet of ivacaftor 25 mg granules once daily or less frequently*

6 months and older, ≥5 kg to <7 kg	No dose adjustment	One sachet of ivacaftor 25 mg granules once daily	Not recommended unless the benefit outweighs the risk. Use with caution as follows: One sachet of ivacaftor 25 mg granules every other day*
6 months and older, ≥7 kg to <14 kg	No dose adjustment	One sachet of ivacaftor 50 mg granules once daily	Not recommended unless the benefit outweighs the risk. Use with caution as follows: One sachet of ivacaftor 50 mg granules every otherday*
6 monthsand older, ≥14 kg to <25 kg	No dose adjustment	One sachet of ivacaftor 75 mg granules once daily	Not recommended unless the benefit outweighs the risk. Use with caution as follows: One sachet of ivacaftor 75 mg granules every other day*
6 months and older, ≥25 kg	No dose adjustment	One tablet of ivacaftor 150 mg once daily	Not recommended unless the benefit outweighs the risk. Use with caution as follows: One tablet of ivacaftor 150 mg every other day*
*Dosing intervals should be modified according to clinical response and tolerability.			

Concomitant use of CYP3A inhibitors

Patients aged 1 month to less than 4 months

Treatment with KALYDECO is not recommended in patients aged 1 month to less than 4 months who are taking concomitant strong or moderate CYP3A inhibitors.

Patients aged 4 months to less than 6 months

Treatment with KALYDECO is not recommended when co-administered with moderate or strong inhibitors of CYP3A in patients aged 4 months to less than 6 months, unless the benefits outweigh the risks. In such cases, the recommended dose is one sachet of 25 mg granules twice weekly or less frequently (see Table 3 and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Dosing

intervals should be modified according to clinical response and tolerability (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Patients aged 6 months and older

When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) in patients aged 6 months and older, KALYDECO should be reduced to one tablet or sachet twice a week based on dosing for the recommended age and weight (see Table 3, Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin) in patients aged 6 months and older, KALYDECO should be reduced to one tablet or sachet once daily based on dosing recommended for the age and weight. (see Table 3, Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 3: Dose adjustment recommendations when co-administered with Mild, Moderate or Strong inhibitors of CYP3A

Age/Weight	Mild CYP3A Inhibitors	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
1 month to less than 4 months, ≥3 kg	No dose adjustment	Not recommended	Not recommended
4 months to less than 6 months, ≥5 kg	No dose adjustment	Not recommended unless the benefit outweighs the risk. Dose as follows in such cases: One sachet of ivacaftor 25 mg granules twice a week, approximately 3 to 4 days apart or less frequently[¥]	Not recommended unless the benefit outweighs the risk. Dose as follows in such cases: One sachet of ivacaftor 25 mg granules twice a week, approximately 3 to 4 days apart or less frequently[¥]
6 months and older, ≥5 kg to <7 kg	No dose adjustment	One sachet of ivacaftor 25 mg granules once daily	One sachet of ivacaftor 25 mg granules twice a week, approximately 3 to 4 days apart
6 months and older, ≥7 kg to <14 kg	No dose adjustment	One sachet of ivacaftor 50 mg granules once daily	One sachet of ivacaftor 50 mg granules twice a week, approximately 3 to 4 days apart

6 months and older, ≥14 kg to <25 kg	No dose adjustment	One sachet of ivacaftor 75 mg granules once daily	One sachet of ivacaftor 75 mg granules twice a week, approximately 3 to 4 days apart
6 months and older, ≥25 kg	No dose adjustment	One tablet of ivacaftor 150 mg once daily	One tablet of ivacaftor 150 mg twice a week, approximately 3 to 4 days apart
¥ Dosing intervals should be modified according to clinical response and tolerability.			

4.3 CONTRAINDICATIONS

In cases of hypersensitivity to the active substance or to any component of these medicines, patients should not be treated with the medicines.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

Patients aged 1 month to less than 4 months

Treatment with ivacaftor is not recommended in patients aged 1 to 4 months with any level of hepatic impairment.

Patients aged 4 months to less than 6 months

No safety data are available in infants aged 4 to less than 6 months of age with moderate or severe hepatic impairment treated with ivacaftor. Treatment with ivacaftor is not recommended in patients aged 4 months to less than 6 months with hepatic impairment, unless the benefits outweigh the risks. In such cases, the starting dose interval should be reduced, and dosing intervals should be modified according to clinical response and tolerability (see Table 2 and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Patients aged 6 months and older

No safety data are available in infants aged 6 to less than 12 months of age with moderate or severe hepatic impairment treated with ivacaftor. A reduced dose of KALYDECO is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).

There is no experience of the use of KALYDECO in patients aged 6 months and older with severe hepatic impairment (Child-Pugh Class C). Use of KALYDECO is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks of over exposure. In such cases, the starting dose interval should be reduced and dosing intervals should be modified according to clinical response and tolerability (see Table 2, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

Interactions with medicinal products

CYP3A inducers

Exposure to ivacaftor is significantly decreased by the concomitant use of CYP3A inducers, potentially resulting in the loss of ivacaftor efficacy; therefore, co-administration of ivacaftor with strong CYP3A inducers is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF

INTERACTIONS).

CYP3A inhibitors

Exposure to ivacaftor is increased when co-administered with strong or moderate CYP3A inhibitors. The dose of ivacaftor must be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see Table 3 and Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). No safety data are available in infants aged 4 to less than 12 months of age who are treated with ivacaftor and moderate or strong CYP3A inhibitors. Treatment with ivacaftor is not recommended in patients aged 1 month to less than 4 months who are taking concomitant strong or moderate CYP3A inhibitors (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in renal impairment
Caution is recommended while using KALYDECO in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly
Clinical studies of ivacaftor did not include a sufficient number of patients aged 65 years and older to evaluate the efficacy and safety of ivacaftor in this age range. Thus, the efficacy and safety of KALYDECO in elderly patients have not been evaluated.

Paediatric use
The efficacy of KALYDECO in patients 1 month to less than 6 years was extrapolated from patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels between patients 1 month to less than 6 years, and adults and children 6 years of age and older. The safety and efficacy of KALYDECO in children aged less than 1 month have not been established.
Efficacy was not demonstrated in patients less than 18 years of age with CF who have an *R117H* mutation in clinical trials. Currently available data are described in Section 5.2 PHARMACOKINETIC PROPERTIES, Section 5 PHARMACOLOGICAL PROPERTIES/CLINICAL TRIALS, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Hypersensitivity Reactions, Including Anaphylaxis
Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the post-marketing 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.

Mood Disturbances
Effects on mood and behaviour such as anxiety, depression, suicidal ideation and behaviour, and insomnia have been reported in people with cystic fibrosis treated with KALYDECO. The events were reported in adult and paediatric patients with and without a previous history of neuropsychiatric symptoms. Symptoms may occur within the first three months of treatment initiation.

In some young children (aged 2-5 years), such effects may manifest as behaviour changes.

Patients and caregivers should be alerted to the need to monitor for new or worsening psychiatric

symptoms and seek medical advice as soon as possible if they occur.

Cataracts
Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor. 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 paediatric patients initiating KALYDECO treatment.

Cataracts were seen in juvenile rats treated with ivacaftor from postnatal day 7-35 at oral doses ≥10 mg/kg/day, yielding exposure to ivacaftor and its major metabolites approximately 3.5-6 times lower than that in patients at the maximum recommended human dose (MRHD) based on summed AUCs. This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

Patients after organ transplantation
KALYDECO has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for interactions with ciclosporin or tacrolimus).

Lactose
KALYDECO contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Effects on laboratory tests
Liver function tests
Moderate transaminase (alanine transaminase [ALT] or aspartate transaminase [AST]) elevations are common in patients with CF. In Studies 1, 2, and 3, the incidence and clinical features of transaminase elevations in clinical trials were similar between patients in the ivacaftor and placebo treatment groups (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In the subset of patients with a medical history of elevated transaminases, increased ALT or AST has been reported more frequently in patients receiving ivacaftor compared to placebo. Therefore, liver function tests are recommended for all patients 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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients who develop unexplained increased transaminase levels during treatment 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, consideration should be given to the continuation of treatment after assessment of the individual benefits and risks.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Medicinal products that inhibit or induce CYP3A activity may impact the pharmacokinetics of ivacaftor. The dose of KALYDECO must be adjusted when concomitantly used with strong and moderate CYP3A inhibitors. Exposure to ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in the loss of efficacy of KALYDECO.

Ivacaftor is a weak CYP3A and P-glycoprotein (P-gp) inhibitor and may modify the pharmacokinetics of medicinal products that are substrates of CYP3A and/or P-gp. *In vitro* studies indicated that ivacaftor has the potential to inhibit CYP2C9.

Medicinal products affecting the pharmacokinetics of KALYDECO

CYP3A inhibitors

Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, increased ivacaftor exposure (measured as area under the curve [AUC]) by 8.5-fold and increased hydroxymethyl-ivacaftor (M1) to a lesser extent than ivacaftor. A reduction of the KALYDECO dose is recommended in patients aged 6 months and older, and only if the benefits outweigh the risks for patients aged 4 months to less than 6 months of age, for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin. Treatment with ivacaftor is not recommended when concomitantly used with strong CYP3A inhibitors in patients aged 1 month to less than 4 months (see Table 3 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold and increased M1 to a lesser extent than ivacaftor. A reduction of the KALYDECO dose is recommended for patients aged 6 months and older, and only if the benefits outweigh the risks for patients aged 4 months to less than 6 months taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin. Treatment with ivacaftor is not recommended when concomitantly used with moderate CYP3A inhibitors in patients aged 1 month to less than 4 months (see Table 3 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Co-administration of KALYDECO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure to ivacaftor. Food containing grapefruit should be avoided during treatment with KALYDECO.

CYP3A inducers

Co-administration of KALYDECO with rifampicin, a strong CYP3A inducer, decreased ivacaftor exposure (AUC) by 89% and decreased M1 to a lesser extent than ivacaftor.

Co-administration with strong CYP3A inducers, such as rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's Wort (*Hypericum perforatum*), is not recommended. Concomitant use of weak to moderate inducers of CYP3A (e.g., dexamethasone, high-dose prednisone) may decrease the exposure of ivacaftor and thus may reduce KALYDECO efficacy.

Other recommendations

Co-administration of ciprofloxacin with KALYDECO did not affect the exposure of ivacaftor. No dose adjustment is required when KALYDECO is co-administered with ciprofloxacin.

Medicinal products affected by KALYDECO

CYP3A, P-gp, or CYP2C9 substrates

Based on *in vitro* results, ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Co-administration with (oral) midazolam, a sensitive CYP3A substrate, increased midazolam exposure 1.5-fold, consistent with weak inhibition of CYP3A by ivacaftor.

Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition by P-gp by ivacaftor. Administration of KALYDECO may increase systemic exposure of medicinal products that are substrates of CYP3A and/or P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Use with caution and monitor for benzodiazepine-related side effects when using concomitant oral midazolam, alprazolam, diazepam, or triazolam. Use with caution and appropriate monitoring when using concomitant digoxin, cyclosporine, or tacrolimus.

Ivacaftor may inhibit CYP2C9. Therefore, monitoring of the INR during co-administration with warfarin is recommended.

Ivacaftor has been studied with an oestrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the oral contraceptive. KALYDECO is not expected to modify the efficacy of oral contraceptives. Therefore, nodose adjustment of oral contraceptives is necessary.

Ivacaftor has been studied with the CYP2C8 substrate rosiglitazone. No significant effect on rosiglitazone exposure was found. Therefore, no dose adjustment of CYP2C8 substrates such as rosiglitazone is necessary.

Ivacaftor has been studied with the CYP2D6 substrate desipramine. No significant effect on desipramine exposure was found. Therefore, no dose adjustment of CYP2D6 substrates such as desipramine is necessary.

Interaction studies have only been performed in healthy adults.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding approximately 10 and 5 times, respectively, the systemic exposure anticipated in patients at the MRHD based on summed AUCs of ivacaftor and its major metabolites) when dams were dosed prior to and during early pregnancy. The pregnancy rate was decreased, oestrus cycling was disrupted and pre-implantation loss was increased. These effects occurred in the presence of significant maternal toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (yielding approximately 6 and 3 times, respectively, the exposure at the MRHD based on summed AUCs of ivacaftor and its metabolites).

Use in pregnancy

Category B3

Category B3 drugs have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There are no adequate and well-controlled studies of KALYDECO in pregnant women. Developmental toxicity studies in animals revealed no teratogenicity in rats at oral doses up to 200 mg/kg/day (yielding 5 times the summed AUC for ivacaftor and its major metabolites anticipated in patients) or in rabbits at up to 100 mg/kg/day (relative exposure based on summed AUCs, ≥3). Fetal weight was decreased, and the incidence of minor fetal skeletal abnormalities was increased in rats treated at 200 mg/kg/day; these effects were observed in conjunction with maternal toxicity. Ivacaftor and/or its metabolites were shown to cross the placenta in rats and rabbits.

As animal reproduction studies are not always predictive of human response, and given the limited experience with KALYDECO in pregnancy, KALYDECO should only be used during pregnancy if the expected benefits to the mother justify the potential risks to the fetus.

Use in lactation

Data from published literature indicate that ivacaftor is present in human milk. There is insufficient information on the effects of ivacaftor on breastfed infants. The safe use of KALYDECO during breast-feeding has not been established. KALYDECO should only be used during breast-feeding if the potential benefit outweighs the potential risk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness has been reported in patients receiving KALYDECO, which could influence the ability to drive or operate machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Trials

The safety profile of KALYDECO is based on seven clinical trials: two pooled, placebo-controlled Phase 3 clinical trials (Study 1 STRIVE and Study 2 ENVISION) conducted in 213 CF patients (109 received ivacaftor and 104 received placebo up to 48 weeks) who had a *G551D* mutation in the *CFTR* gene; a 96-week open-label extension study (Study 4 PERSIST) that included 192 patients with a *G551D* mutation; an 8-week, Phase 3, placebo-controlled crossover design study (Study 5 KONNECTION) in 39 patients with CF who had a *non-G551D* gating (class III) mutation in the *CFTR* gene; a 24-week, placebo-controlled trial (Study 6 KONDUCT) involving 69 patients with an *R117H* mutation in the *CFTR* gene; and a 24-week, open-label study (Study 7 KIWI) that included34 patients with a *G551D* or another gating (class III) mutation in the *CFTR* gene; and a cohort of 19 patients aged 12 months to less than 24 months, a cohort of 11 patients aged 6months to less than 12 months, a cohort of 6 patients aged 4 months to less than 6 months and a cohort of 7 patients aged 1 to less than 4 months in a 24-week, open-label, Phase 3 clinical study in patients with CF (Study 8 ARRIVAL). Patients with a gating mutation or *R117H* mutation were eligible for this study. Patients with any ivacaftor responsive mutations were eligible for the cohort aged 1 to less 4 months cohort of this study. Patients treated with KALYDECO in these trials were between the ages of 1 month and 68 years.

The most common adverse reactions that were more frequent in patients with a *G551D* mutation who received ivacaftor for 48 weeks in the placebo-controlled Phase 3 trials were abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo), upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) (63.3% versus 50.0% on placebo), headache (23.9% versus 16.3% on placebo) and bacteria in sputum (7.3% versus 3.8% on placebo). One patient in the ivacaftor group reported a serious adverse reaction: abdominal pain.

Adverse events were identified based on the pooled data of the 48-week, placebo-controlled Studies 1 (STRIVE) and 2 (ENVISION) in patients aged 6 years and older who had a *G551D* mutation in the *CFTR* gene.

Table 4 shows adverse events with an incidence of at least 10% in any treatment group from the two double-blind, placebo-controlled Phase 3 trials.

Table 4: Adverse Events with an Incidence of at Least 10% in any Treatment Group of Patients Aged 6 Years and Older with the *G551D* Mutation in the *CFTR* Gene

Preferred Term	KALYDECO N=109 n (%)	Placebo N=104 n (%)
Cystic fibrosis lung	42 (38.5)	58 (55.8)
Cough	40 (36.7)	52 (50.0)
Headache	26 (23.9)	17 (16.3)
Oropharyngeal pain	24 (22.0)	19 (18.3)

Upper respiratory tract infection	24 (22.0)	14 (13.5)
Nasal congestion	22 (20.2)	16 (15.4)
Abdominal pain	17 (15.6)	13 (12.5)
Pyrexia	16 (14.7)	16 (15.4)
Nasopharyngitis	16 (14.7)	12 (11.5)
Productive cough	14 (12.8)	16 (15.4)
Diarrhoea	14 (12.8)	10 (9.6)
Rash	14 (12.8)	7 (6.7)
Nausea	13 (11.9)	11 (10.6)
Vomiting	11 (10.1)	17 (16.3)
Rales	11(10.1)	12 (11.5)
Hemoptysis	9 (8.3)	17 (16.3)
Pulmonary function test decreased	5 (4.6)	15 (14.4)
Abdominal pain upper	10 (9.2)	11 (10.6)

Table 5 presents the adverse reactions identified in patients aged 6 years and older who had a *G551D* mutation in at least one allele listed by system organ class, preferred term, and frequency. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (frequency cannot be estimated using the available data).

Table 5: Adverse Reactions in KALYDECO-treated Patients Aged 6 Years and Older with the *G551D* Mutation in the *CFTR* Gene

System Organ Class	Frequency Category	Adverse Reactions (Preferred term) KALYDECO N=109
Infections and infestations	very common	Nasopharyngitis
	very common	Upper respiratory tract infection
	common	Rhinitis
Nervous system disorders	very common	Headache
	common	Dizziness
Ear and labyrinth disorders	common	Ear discomfort
	common	Ear pain
	common	Tinnitus
	common	Tympanic membrane hyperaemia
	uncommon	Ear congestion
	uncommon	Vestibular disorder
Respiratory, thoracic, and mediastinal disorders	very common	Nasal congestion
	very common	Oropharyngeal pain
	common	Pharyngeal erythema
	common	Sinus congestion
Gastrointestinal disorders	very common	Abdominal pain
	very common	Diarrhoea
Skin and subcutaneous tissue disorders	very common	Rash
Reproductive system and	uncommon	Breast inflammation

breast disorders	uncommon	Breast mass
	uncommon	Gynaecomastia
	uncommon	Nipple disorder
	uncommon	Nipple pain
Investigations	common	Bacteria in sputum

Description of Selected Adverse Reactions

Rash
During 48-week, placebo-controlled clinical trials, the incidence of rash was 12.8% in KALYDECO-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of rash.

Ear and Labyrinth Disorders
During 48-week, placebo-controlled clinical trials, the incidence of ear and labyrinth disorders was 9.2% in KALYDECO-treated patients. Most events were described as mild to moderate in severity, one event of ear pain was described as severe, none were serious, and no patients discontinued treatment because of ear and labyrinth disorder.

Nervous System Disorders
Headache
During 48-week, placebo-controlled clinical trials, the incidence of headache was 23.9% in KALYDECO-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of headache.

Dizziness
During 48-week, placebo-controlled clinical trials, the incidence of dizziness was 9.2% in the KALYDECO-treated patients. Including data from all clinical trial and post-marketing data, most of these events were non-serious and most of these patients did not discontinue the treatment because of dizziness.

Upper Respiratory Tract Reactions
During 48-week, placebo-controlled clinical trials, the incidence of upper respiratory tract reactions (upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) was 63.3% in KALYDECO-treated patients. Most events were described as mild to moderate in severity, one event of upper respiratory tract infection and one event of nasal congestion were considered to be severe, none were serious, and no patients discontinued treatment because of upper respiratory tract reactions.

Laboratory Abnormalities
Transaminase elevations
During the placebo-controlled Studies 1 (STRIVE), 2 (ENVISION), and 3 (DISCOVER), up to 48 weeks, in patients with a *G551D* mutation in the *CFTR* gene or who were homozygous for the *F508del* mutation, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 1.8%, 2.3%, and 5.9% in KALYDECO-treated patients and 1.5%, 2.3%, and 8.3% in placebo-treated patients, respectively. Three patients, 2 (1.5%) on placebo and 1 (0.5%) on KALYDECO, permanently discontinued treatment for elevated transaminases, which were all >8 x ULN. No KALYDECO-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >1.5 x ULN. In KALYDECO-treated patients, most transaminase elevations up to 5 x ULN resolved

without treatment interruption. KALYDECO dosing was interrupted in most patients with transaminase elevations >5 x ULN. In all instances where dosing was interrupted for elevated transaminases, KALYDECO dosing was able to be resumed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

LONG-TERM SAFETY (STUDY 4-VX08-770-105, PERSIST): Open-Label Extension Study in Patients ≥6 years

Among 192 patients with the *G551D* mutation treated with KALYDECO for 96 weeks in an open-label extension study (Study 4 PERSIST) following the placebo-controlled Phase 3 studies (96 to 144 weeks cumulatively), the nature of adverse events was similar to those reported in the placebo-controlled Phase 3 studies. Serious adverse reactions observed during the 96-week extension study included abdominal pain (1%), headache (1%), and vestibular disorder (0.5%).

***Non-G551D* Gating Population (Study 5 - VX12-770-111, KONNECTION): Study in Patients (≥6 years) with CF with *non-G551D* Gating Mutations)**

In an 8-week, two-part, randomised, double-blind, placebo-controlled, crossover Phase 3 clinical trial of 39 patients with CF aged 6 and older who had a *non-G551D* gating mutation in the *CFTR* gene (Study 5 KONNECTION), the safety results were consistent with those observed in studies in patients with CF who had the *G551D* mutation. In the *non-G551D* gating population, one adverse reaction occurred in more patients during treatment with KALYDECO, compared with placebo: rhinitis (7.9% versus 5.4% on placebo).

***R117H* Population (Study 6 - (VX11-770-110, KONDUCT): Study in Patients with CF with an *R117H* Mutation in the *CFTR Gene*)**

In a 24-week, placebo-controlled trial (Study 6 KONDUCT) involving 69 patients with CF aged 6 years and older who had an *R117H* mutation in the *CFTR* gene, the safety results were consistent with those observed in studies in patients with CF who had the *G551D* mutation.

Paediatric Population

The safety data were evaluated in 6 patients aged 4 months to less than 6 months, 11 patients aged 6 months to less than 12 months, 19 patients aged 12 months to less than 24 months, 34 patients aged 2 years to less than 6 years of age, 52 patients between 6 to less than 12 years of age and 93 patients between 12 to less than 18 years of age. The safety profile is generally consistent among children and adolescents and is also consistent with adult patients.

Paediatric Safety and Efficacy Study in patients aged 2 to less than 6 years of age (Study 7 - VX11-770-108, KIWI): Study in Paediatric Patients with CF aged 2 to less than 6 years with *G551D* or another gating mutation)

In this paediatric population transaminase elevation and vomiting were observed more frequently as compared to the adults; however, it is unknown if these effects were due to KALYDECO. In this study the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of ivacaftor dosing. Ivacaftor was discontinued permanently in one patient (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Liver function tests*).

Paediatric Safety Study in patients aged 4 months to < 24 months (Study 8 - VX15-770-124, ARRIVAL): Safety Study in Paediatric Patients with CF aged less than 24 months

Patients aged 12 months to less than 24 months

During the 24-week, open-label, Phase 3 clinical study in 19 patients aged 12 months to less than 24 months, the incidence of patients experiencing transaminase elevations (ALT or AST) >3, >5, and >8 x ULN was 27.8% (5/18), 11.1% (2/18) and 11.1% (2/18),

respectively. No patients had elevations in total bilirubin. No subjects discontinued ivacaftor treatment due to transaminase elevations. The two patients with elevations of ALT or AST >8 x ULN interrupted treatment and subsequently resumed ivacaftor successfully.

Patients aged 4 months to less than 12 months

In the cohort of patients aged 6 months to less than 12 months (N=11) one patient (9.1%) had elevated ALT of >3 to ≤5 x ULN. In the cohort of patients aged 4 months to less than 6 months (N=6), no patients had elevated ALT or AST (>3 x ULN). No patients had elevations in total bilirubin or discontinued ivacaftor treatment due to transaminase elevations in this cohort.

Patients aged 1 month to less than 4 months

In the cohort of patients aged 1 month to less than 4 months (N=7), 1 patient (14.2%) had maximum ALT or AST >3 x ULN (ALT >8 x ULN and AST of >3 to ≤5 x ULN); the subject discontinued ivacaftor treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, management of elevated transaminases).

Post-Marketing Experience
The following adverse reactions have been identified during post approval use of KALYDECO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: anaphylaxis.

Psychiatric Disorders: anxiety, depression, suicidal ideation or behaviour, insomnia.

Reporting Suspected Adverse Effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

The highest repeated dose was 450 mg (in a tablet formulation) every 12 hours for 4.5 days (9 doses) in a trial evaluating the effect of KALYDECO on ECGs in healthy subjects. Adverse events reported at a higher incidence compared to placebo included dizziness and diarrhoea.

No specific antidote is available for overdose with KALYDECO. Treatment of overdose with KALYDECO consists of general supportive measures including monitoring of vital signs, liver function tests, and observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Ivacaftor is a selective potentiator of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. *In vitro*, ivacaftor increases the open probability of the CFTR channel gate to enhance chloride transport. This has been demonstrated in normal CFTR and in mutant forms of CFTR that have reduced channel-open probability, such as *G551D-*

CFTR and *R117H-CFTR*. The exact mechanism leading ivacaftor to prolong the gating activity of some mutant CFTR forms has not been completely elucidated.

The chloride transport response of mutant CFTR protein to ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of Fisher Rat Thyroid (FRT) cell lines transfected with individual cell mutations. Ivacaftor increases chloride transport in FRT cells expressing *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

The *in vitro* CFTR chloride transport response threshold was designated as at least a 10% net increase in chloride transport over baseline as a percent of normal CFTR because it is predictive or reasonably expected to predict clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

The *G970R* mutation was previously classified as a gating mutation; however, it was found to cause a splicing defect resulting in little-to-no CFTR protein at the cell surface.

Table 6 lists mutations that are responsive to ivacaftor based on 1) a positive clinical response and/or 2) *in vitro* data in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal).

Table 6: *CFTR* gene mutations that produce CFTR protein and are responsive to ivacaftor

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

*Clinical data exist for these mutations [see Clinical efficacy].
† 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.

In clinical trials (Study 1 STRIVE and Study 2 ENVISION) in patients with the *G551D* mutation in one allele of the *CFTR* gene administered 150 mg of ivacaftor tablets every 12 hours, Study 1 STRIVE in patients aged 12 years and older and Study 2 ENVISION in patients 6 to 11 years of age, ivacaftor led to rapid (15 days), substantial (the mean change in sweat chloride from baseline through Week 24 was -48 mmol/L [95% CI -51, -45] and -54 mmol/L [95% CI -62, -47] respectively), and sustained (through 48 weeks) reduction in sweat chloride concentration.

In a clinical trial in patients aged 6 years and older administered 150 mg of ivacaftor tablets every 12 hours who had a non-G551D gating mutation in the *CFTR* gene (Study 5 KONNECTION, Part 1), treatment with ivacaftor led to a rapid (15 days) and substantial mean change in sweat chloride from baseline of -49 mmol/L (95% CI -57, -41) after 8 weeks of treatment. However, in patients with the *G970R-CFTR* mutation, the mean (SD) absolute change in sweat chloride at Week 8 was -6.25 (6.55) mmol/L. Clinical efficacy has not been established in patients with the *G970R* mutation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In a clinical trial (Study 6 KONDUCT) in 69 patients aged 6 years or older with CF who had an *R117H* mutation in the *CFTR* gene, the treatment difference in mean change in sweat chloride from baseline through 24 weeks of treatment was -24 mmol/L (95% CI -28, -20) and in patients 18 years or older it was -22 mmol/L (95% CI -26, -17). The mean sweat chloride change was consistent across subgroups, including age, poly-T status, and FEV_1.

In an open-label, Phase 3 clinical study in 34 patients aged 2 to less than 6 years with *G551D* or another gating mutation, administered either 50 mg or 75 mg of ivacaftor granules every 12 hours (Study 7 KIWI), the mean absolute change from baseline in sweat chloride was -47 mmol/L (95% CI -58, -36) at Week 24.

In a 24-week, open-label, Phase 3 clinical study in patients with CF aged less than 24 months with a gating mutation or an *R117H* mutation (Study 8 ARRIVAL), the mean absolute change from baseline in sweat chloride for patients aged 12 months to less than 24 months (n=10) was -73.5 mmol/L (SD: 17.5) at Week 24. The mean absolute change from baseline in sweat chloride for patients aged 6 months to less than 12 months (n=6) was -58.6 mmol/L (SD: 16.5) at Week 24, and the mean absolute change from baseline in sweat chloride for patients aged 4 months to less than 6 months (n=3) was -50 mmol/L (SD: 17.3) at Week 24. The mean absolute change from baseline in sweat chloride through 24 weeks for patients aged 1 month to less than 4 months (N=5) was -40.3 mmol/L (SD: 29.2). Patients with a gating mutation or *R117H* mutation were eligible for all cohorts of this study, and patients with an ivacaftor-responsive mutations were eligible for the cohort aged 1 month to less than 4 months.

Clinical Trials
The efficacy of KALYDECO has been evaluated in eight clinical trials including two Phase 3, randomised, double-blind, placebo-controlled, multi-centre studies of clinically stable patients with CF who had the *G551D* mutation in the *CFTR* gene on at least 1 allele and had FEV_1 (forced expiratory volume exhaled in the first second) ≥40% predicted.

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

Efficacy results from a Phase 2 study in patients with CF who were homozygous for the *F508del* mutation in the *CFTR* gene (Study 3 DISCOVER) showed no statistically significant difference in FEV_1 over 16 weeks of ivacaftor treatment compared to placebo. Therefore, use of KALYDECO in these patients is not recommended.

Study 1 (VX08-770-102, STRIVE): Study in Patients with CF (≥12 years) with a *G551D-CFTR* Mutation
Study 1 STRIVE evaluated 161 patients who were 12 years of age or older; 122 (75.8%) patients had the *F508del* mutation in the second allele. At the start of the study, patients in the placebo group used some medicinal products at a higher frequency than the ivacaftor group.

These medications included dornase alfa (73.1% versus 65.1%), salbutamol (53.8% versus

42.2%), tobramycin (44.9% versus 33.7%), and salmeterol/fluticasone (41.0% versus 27.7%). At baseline, mean predicted FEV_1 was 63.6% (range: 31.6% to 98.2%) and mean age was 26 years (range: 12 to 53 years).

Study 2 (VX08-770-103, ENVISION): Study in Patients with CF (6 to 11 years) with a *G551D-CFTR* Mutation

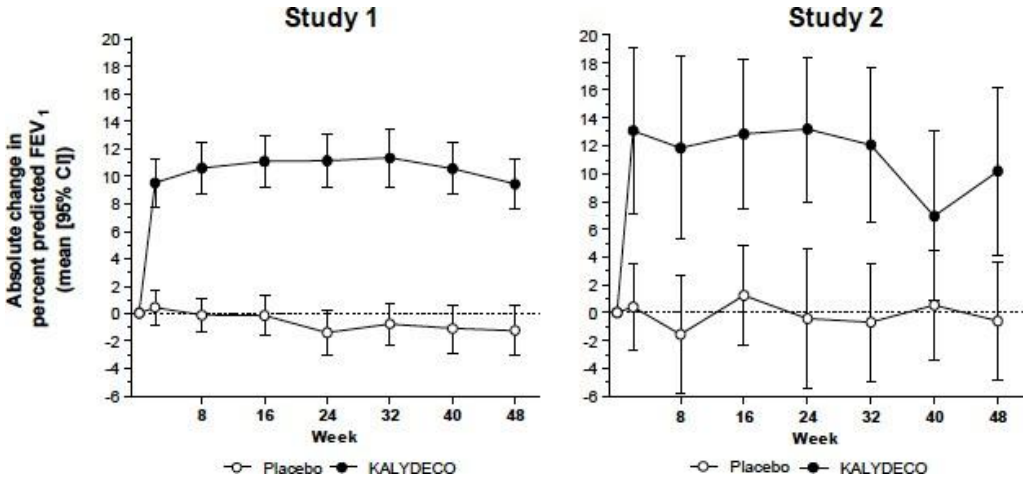
Study 2 ENVISION evaluated 52 patients who were 6 to 11 years of age at screening; mean (SD) body weight was 30.9 (8.63) kg; 42 (80.8%) of patients had the *F508del* mutation in the second allele. At baseline, mean predicted FEV_1 was 84.2% (range: 44.0% to 133.8%) and mean age was 9 years (range: 6 to 11 years); 8 (30.8%) patients in the placebo group and 4 (15.4%) patients in the ivacaftor group had an FEV_1 less than 70% predicted at baseline.

The primary efficacy endpoint in both studies was the mean absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment.

The treatment difference between ivacaftor and placebo for the mean absolute change (95% CI) in percent predicted FEV_1 from baseline through Week 24 was 10.6 percentage points (8.6, 12.6) in Study 1 STRIVE and 12.5 percentage points (6.6, 18.3) in Study 2 ENVISION (Figure 1).

The treatment difference between ivacaftor and placebo for the mean relative change (95% CI) in percent predicted FEV_1 from baseline through Week 24 was 17.1% (13.9, 20.2) in Study 1 STRIVE and 15.8% (8.4, 23.2) in Study 2 ENVISION. The mean change from baseline through Week 24 in FEV_1 (L) was 0.37 L in the ivacaftor group and 0.01 L in the placebo group in Study 1 STRIVE and 0.30 L in the ivacaftor group and 0.07 L in the placebo group in Study 2 ENVISION. In both studies, improvements in percent predicted FEV_1 were rapid in onset (Day 15 $P<0.0001$ and $P=0.0004$ for Study 1 STRIVE and Study 2 ENVISION, respectively) and durable through 48 weeks ($P<0.0001$ and $P=0.0017$ for Study 1 STRIVE and Study 2 ENVISION, respectively).

Figure 1: Mean Absolute Change from Baseline in Percent Predicted FEV_1



FEV_1 results at 24 and 48 weeks by age subgroups are shown in Table 7.

Table 7: Mean Absolute Change from Baseline in Percent Predicted FEV_1 by Age in MMRM Analysis			
Subgroup Age (years)	**Study**	**Through Week 24 (percentage points) (95% CI)**	**Through Week 48 (percentage points) (95% CI)**
6 to 11	2	12.5 (6.6, 18.3)	10.0 (4.5, 15.5)
12 to 17	1	11.9 (5.9, 17.9)	11.4 (5.4, 17.4)
≥18	1	9.9 (7.8, 12.0)	9.9 (7.7, 12.0)
CI: confidence interval; FEV_1: forced expiratory volume in 1 second; MMRM: mixed-effects model for repeated measures			

The results for clinically relevant secondary endpoints are shown in Table 8.

Table 8: Effect of Ivacaftor on Other Efficacy Endpoints in Study 1 STRIVE and Study 2 ENVISION				
	Study 1 STRIVE		**Study 2 ENVISION**	
Endpoint	**Treatment difference[a] (95% CI)**	***P* value**	**Treatment difference [a](95% CI)**	***P* value**
Mean absolute change from baseline in CFQ-R[b] respiratory domain score (points)[c]				
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[d]	0.0016	NA	NA
Through Week 48	0.46[d]	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
Mean absolute change from baseline in BMI (kg/m^2)				
At Week 24	0.94 (0.62, 1.26)	<0.0001	0.81 (0.34, 1.28)	0.0008
At Week 48	0.93 (0.48, 1.38)	<0.0001	1.09 (0.51, 1.67)	0.0003
Mean change from baseline in z-scores				
Weight-for-age z-score at Week 48[e]	0.33 (0.04, 0.62)	0.0260	0.39 (0.24, 0.53)	<0.0001
BMI-for-age z-score at Week 48[e]	0.33 (0.002, 0.65)	0.0490	0.45 (0.26, 0.65)	<0.0001

CI: confidence interval; NA: not analysed due to low incidence of events

[a] Treatment difference = effect of ivacaftor – effect of placebo

[b] CFQ-R: Cystic Fibrosis Questionnaire-Revised is a disease-specific, health-related quality-of-life measure for CF. Minimum Clinically Important Difference (MCID)=4 units.

[c] Study 1 STRIVE data were pooled from CFQ-R for adults/adolescents and CFQ-R for children 12 to 13 years of age; Study 2 ENVISION data were obtained from CFQ-R for children 6 to 11 years of age.

[d] Hazard ratio for time to first pulmonary exacerbation

[e] In patients under 20 years of age (CDC growth charts)

Study 3 (VX08-770-104, DISCOVER): Study in Patients (≥12 years) with CF with the *F508del* Mutation in *CFTR* Gene

Study 3 DISCOVER (Part A) was a 16-week, 4:1 randomised, double-blind, placebo-controlled, parallel-group, Phase 2 study of ivacaftor (150 mg tablets every 12 hours) in 140 patients with CF aged 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who had FEV_1 ≥40% predicted.

The mean absolute change from baseline through Week 16 in percent predicted FEV_1 (primary efficacy endpoint) was 1.5 percentage points in the ivacaftor group and -0.2 percentage points in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 1.7 percentage points (95% CI -0.6, 4.1); this difference was not statistically significant (P=0.15).

Study 4 (VX08-770-105, PERSIST): Open-Label Extension Study in Patients ≥6 years
Study 4 PERSIST is an open-label extension study to evaluate the safety and efficacy of long-term treatment of orally administered ivacaftor (150 mg tablets every 12 hours) in patients continuing from Studies 1 and 2. It enrolled 144 adolescents/adults who completed Study 1 STRIVE (age ≥12 years) and 48 children who completed Study 2 ENVISION (age 6 to 11 years). The percent predicted FEV_1 range at the beginning of Study 4 PERSIST was 29.1% to 126.7%. The use of inhaled hypertonic saline was permitted. A pre-specified analysis of all patients' data was performed after all patients from Study 1 STRIVE and Study 2 ENVISION who had not discontinued received 96 weeks of treatment with ivacaftor in Study 4 (for a total exposure of 144 weeks for patients who received ivacaftor in Study 1 STRIVE and Study 2 ENVISION).

In Study 4 PERSIST, the substantial lung function improvement and weight gain (as seen in Study 1 STRIVE and Study 2 ENVISION) (Table 9) and CFQ-R changes (as seen in Study 1 STRIVE) persisted through 144 weeks of cumulative ivacaftor treatment. The time-to-first pulmonary exacerbation showed a consistent trend across 144 weeks for patients treated with ivacaftor from Study 1 STRIVE. Too few patients experienced pulmonary exacerbations in Study 2 ENVISION to perform a meaningful statistical analysis.

Table 9: Effect of Ivacaftor in Study 4 PERSIST

Original study and treatment group	Duration of ivacaftor treatment (weeks)	Absolute change in percent predicted FEV_1 (percentage points)		Absolute change in body weight (kg)	
		N	Mean (SD)	N	Mean (SD)
Study 1 STRIVE					
Ivacaftor	48*	77	9.4 (8.3)	77	3.4 (4.9)
	144	72	9.4 (10.8)	72	4.1 (7.1)
Placebo	0*	67	-1.2 (7.8)†	67	0.3 (2.7)†
	96	55	9.5 (11.2)	55	3.0 (4.7)
Study 2 ENVISION					
Ivacaftor	48*	26	10.2 (15.7)	26	6.1 (2.9)
	144	25	10.3 (12.4)	25	14.8 (5.7)
Placebo	0*	22	-0.6 (10.1)†	22	2.9 (1.8)†
	96	21	10.5 (11.5)	21	10.1 (4.1)

* Treatment occurred during blinded, controlled, 48-week, Phase 3 study.
† Change from prior study baseline after 48 weeks of placebo treatment.

Figure 2: Mean Absolute Change in Percent Predicted FEV_1 from Baseline in Study 1 STRIVE and Study 2 ENVISION to Week 144 in Study 4 PERSIST

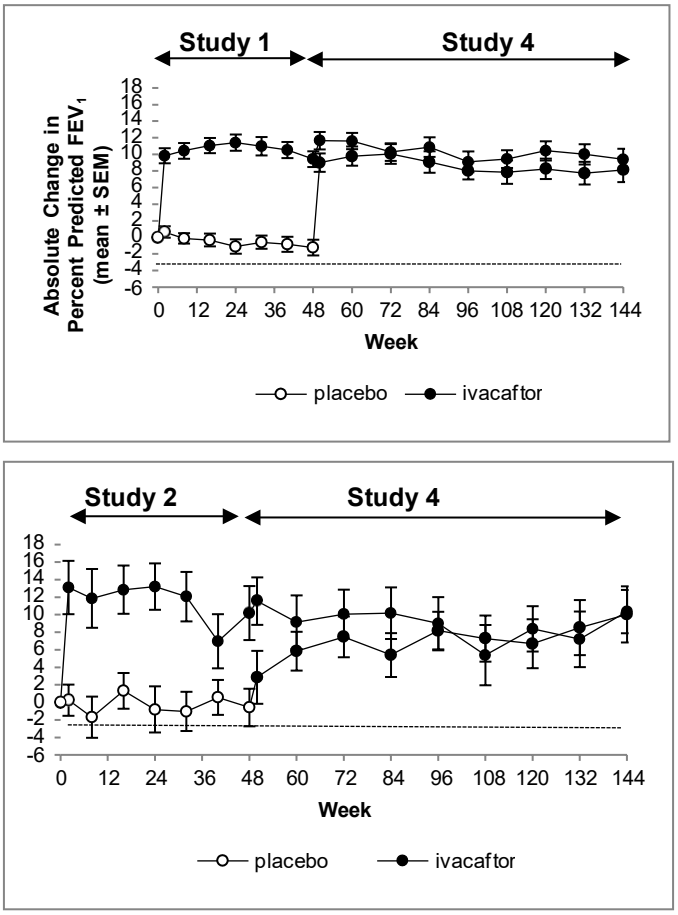


Figure 3: Absolute Change in Weight in Study 1 STRIVE and Study 2 ENVISION to Week 144 in Study 4 PERSIST

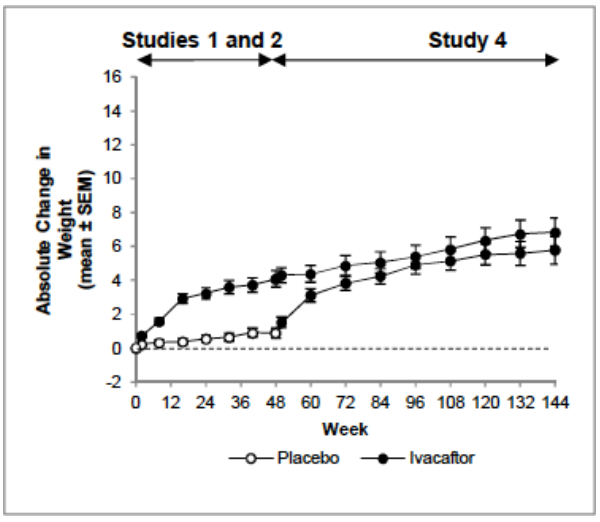
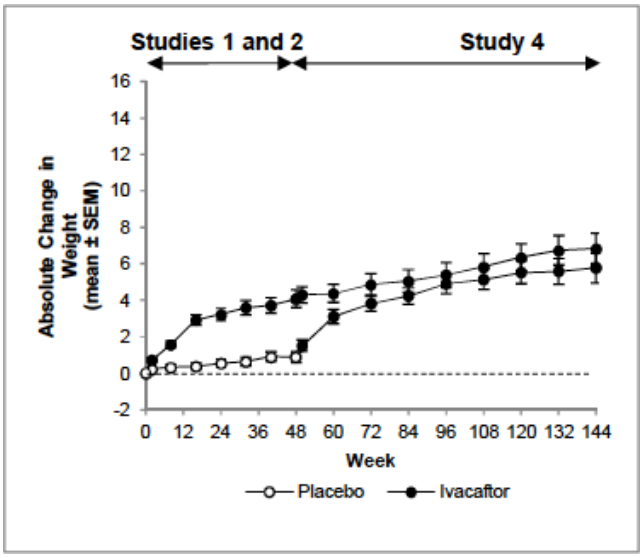
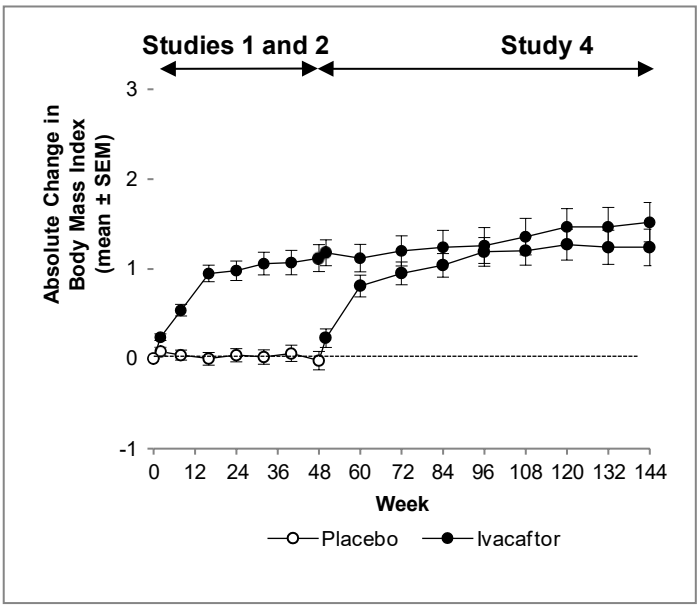


Figure 4: Absolute Change in Body Mass Index (BMI) in Study 1 STRIVE and Study 2 ENVISION to Week 144 in Study 4 PERSIST





Study 5 (VX12-770-111, KONNECTION): Study in Patients (≥6 years) with CF with *non-G551D* Gating Mutations

Study 5 KONNECTION was a Phase 3, two-part, randomised, double-blind, placebo-controlled, crossover study (Part 1) with an open-label extension period (Part 2) to evaluate the efficacy and safety of ivacaftor in patients with CF who have a *non-G551D* gating mutation in the *CFTR* gene (*G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*). Patients who completed Part 1 of this study (randomised, double-blind, placebo-controlled, 8-week crossover) continued into the 16-week open-label Part 2 of the study. Four patients with a *G970R* mutation were also represented in this study. Clinical efficacy in patients with the *G970R* mutation could not be established.

Study 5 KONNECTION evaluated 39 patients with CF who were 6 years of age or older (mean age 23 years) with baseline FEV_1 ≥40% predicted (mean FEV_1 78% predicted [range: 43% to 119%]).

In Part 1, patients were randomised 1:1 to receive either 150 mg of ivacaftor tablets or

placebo every 12 hours with fat-containing food 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.

In Part 1 of Study 5 KONNECTION, the observed treatment difference between ivacaftor and placebo for the mean absolute change in percent predicted FEV_1 from baseline through Week 8 was 10.7 percentage points (P<0.0001). Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, geographic region, and *Pseudomonas aeruginosa* infection status at baseline. Improvement in percent predicted FEV_1 was rapid in onset (Day 15, P<0.0001) and durable through 8 weeks (P<0.0001) of treatment with ivacaftor.

Treatment with ivacaftor resulted in substantial, consistent, and statistically significant treatment effects across the secondary endpoints of the absolute change from baseline in BMI and BMI-for-age z-score at Week 8 was 0.7 kg/m^2 (P<0.0001) and 0.3 points (P=0.0010), respectively, and CFQ-R respiratory domain score through Week 8 was 9.6 points (P=0.0004; Minimum Clinically Important Difference=4 units) when compared to placebo. Together, these results demonstrate the positive effects of ivacaftor treatment on pulmonary and extrapulmonary measures.

Study 6 (VX11-770-110, KONDUCT): Study in Patients with CF with 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 randomised, double-blind, placebo-controlled, parallel-group clinical trial of patients aged 6 years and older with cystic fibrosis. Fifty-nine of 69 patients completed 24 weeks of treatment. Two patients discontinued and 8 patients did not complete treatment due to study termination. 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 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 randomised 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. The treatment difference in mean change in sweat chloride from baseline through 24 weeks of treatment was -24 mmol/L (95% CI -28, -20) and in patients 18 years or older it was -22 mmol/L (95% CI -26, -17). The mean sweat chloride change was consistent across subgroups, including age, poly-T status, and FEV_1.

In a subgroup analysis in patients aged 18 years and older, the treatment difference for the mean absolute change from baseline through Week 24 in percent predicted FEV_1 was 5.0 percent points (95% CI 1.1, 8.8). In a subgroup analysis in patients 6-11 years of age, the treatment difference for the mean absolute change from baseline through Week 24 in percent predicted FEV_1 was -6.3 percentage points (95% CI -12.0, -0.7).

No statistical analysis was conducted for subjects 12 to 17 years of age because only 2 patients were enrolled in the clinical study (Table 10).

Other efficacy variables that were analysed 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 10), 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. Subgroups analyzed included those based on age, lung function, and poly-T status (Table 10).

Table 10: 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 Randomised 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										
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

The efficacy of ivacaftor beyond 2 years of treatment has not been examined in clinical trials in children with *R117H* mutation.

Study 7 (VX11-770-108, KIWI): Study in Paediatric Patients with CF aged 2 to less than 6 years with *G551D* or another gating mutation

The pharmacokinetic profile, safety and efficacy of ivacaftor granules in patients aged 2 through less than 6 years with CF who have a *G551D* mutation or other gating (class III) mutation in the *CFTR* gene were studied in a 2-part, 24-week, open-label, Phase 3 clinical

study in 34 patients (efficacy was a tertiary endpoint). The results of studies 1, 2 and 5 which examined ivacaftor in older subjects were used as supportive data.

Patients in Study 7 KIWI were 2 to less than 6 years of age (mean age 3 years). The majority of the study population had pancreatic insufficiency; 25 of the 27 patients with available data had Faecal Elastase-1 values <50 µg/g at baseline. The mean Faecal Elastase-1 value at baseline was 28 µg/g.

Patients with evidence of colonisation 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 x ULN at screening were excluded.

Patients were assigned to the ivacaftor 50 mg or ivacaftor 75 mg groups according to their weight at enrolment (patients weighing less than 14 kg received ivacaftor 50 mg granules and patients weighing more than 14 kg received ivacaftor 75 mg granules). Ivacaftor was administered orally every 12 hours with fat-containing food in addition to their prescribed CF therapies.

Efficacy endpoints evaluated were absolute change from baseline in sweat chloride through 24 weeks of treatment, measures of nutritional status including absolute change from baseline in weight, body mass index (BMI), and stature (supported by weight, BMI, and stature-for-age z-scores) at 24 weeks of treatment, and measures of pancreatic function including Faecal Elastase-1 and Immunoreactive Trypsinogen (IRT) results at 24 weeks.

Overall, sweat chloride, and mean absolute changes from baseline in nutritional status (weight, BMI, stature; supported by weight, BMI, and stature-for-age z-scores), showed improvement from baseline in Study 7 KIWI. Changes in weight and BMI z-scores are consistent with results shown in 6- to 11-year-olds in Study 2 ENVISION and Study 5 KONNECTION. Substantial increases from baseline in Faecal Elastase-1 were observed at Week 24. The mean (SD) overall change from baseline in Faecal Elastase-1 (n=27) was 99.8 µg/g (138.4). Six patients with initial levels below 200 µg/g achieved, at Week 24, a level of ≥200 µg/g. Changes from baseline in IRT (mean baseline value 33.58 ng/mL) showed decreases at Week 24. Results are shown in Table 11. Data on percent predicted FEV_1 (exploratory endpoint) were available for 3 patients in the ivacaftor 50 mg group and 17 patients in the 75 mg dosing group. The mean (SD) overall change in percent predicted FEV_1 from baseline at Week 24 (exploratory endpoint) was 1.8 (17.81).

Table 11: Effect of Ivacaftor on Efficacy Endpoints in Study 7 KIWI			
	Week 24 Mean (SD) Absolute Changes From Baseline		
Endpoint	**Ivacaftor 50 mg (N=10)**	**Ivacaftor 75 mg (N=24)**	**Overall (N=34)**
Secondary Endpoints			
Weight (kg)	1.0 (0.42)	1.5 (0.55)	1.4 (0.56)
BMI (kg/m^2)	0.33 (0.54)	0.31 (0.55)	0.32 (0.54)
Stature (cm)	2.5 (1.45)	3.5 (0.93)	3.3 (1.17)
Other Endpoints			
Weight-for-age z-scores(unit)	0.18 (0.32)	0.21 (0.23)	0.20 (0.25)
BMI-for-age z-scores (unit)	0.46 (0.46)	0.34 (0.42)	0.37 (0.42)
Stature-for-age z-scores (unit)	-0.25 (0.45)	0.08 (0.22)	-0.01 (0.33)
Faecal Elastase-1 (µg/g)*	128 (191.84)	93.5 (128.28)	99.8 (138.35)
Immunoreactive Trypsinogen (IRT)†	-24.37 (21.71)	-19.54 (25.11)	-20.70 (23.99)
* N=5, ivacaftor 50 mg; N=22, ivacaftor 75 mg; N=27, overall † N=7, ivacaftor 50 mg; N=21, ivacaftor 75 mg; N=28, overall			

Study 8 (VX15-770-124, ARRIVAL): Safety Study in Paediatric Patients with CF aged less than 24 months

The use of ivacaftor in patients with CF aged 1 month to less than 24 months is based on the extrapolation of evidence from studies of ivacaftor in patients aged 6 years and older, and supported by additional PK and safety data from clinical trial (Study 8 ARRIVAL). Study 8 ARRIVAL was a 24-week open-label, Phase 3 clinical study including data of a cohort of 19 patients aged 12 months to less than 24 months, a cohort of 11 patients aged 6 months to less than 12 months, a cohort of 6 patients aged 4 months to less than 6 months and a cohort of 7 patients aged 1 to less than 4 months. Patients with a gating mutation, or *R117H* mutation were eligible to participate in all cohorts of this study and patients with an ivacaftor-responsive mutation were eligible for the cohort aged 1 month to less than 4 months.

In Part B of Study 8 ARRIVAL, patients received ivacaftor 25 mg, 50 mg or 75 mg according to their age and weight at each study visit (patients weighing 5 kg to less than 7 kg received ivacaftor 25 mg, patients weighing 7 kg to less than 14 kg received ivacaftor 50 mg, and patients weighing more than 14 kg received ivacaftor 75 mg). Part A/B of Study 8 ARRIVAL cohort 8 enrolled 7 patients aged 1 month to less than 4 months (mean age 1.9 months at baseline) with 6 patients completing the 24-week treatment period. Patients in Part A/B received an initial low dose of ivacaftor (5.7 mg or 11.4 mg) based on their age and weight on Day 1. Dosing was maintained or adjusted on Day 15 to either 5.7 mg, 11.4 mg, 17.1 mg, 22.8 mg, or 25 mg based on their Day 4 pharmacokinetics. Subjects remained on their Day 15 dose until they reached 4 months of age and at least 5 kg, after which the recommended age- and weight-appropriate dose(s) was administered. Ivacaftor was administered orally every 12 hours with fat-containing food in addition to standard-of-care CF therapies.

The primary endpoint of safety was evaluated through 24 weeks (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Secondary endpoints were evaluation of pharmacokinetics and the absolute change from baseline in sweat chloride. Sweat chloride showed improvement from baseline as early as Week 2, which was sustained through 24 weeks of treatment. Mean measures of nutritional status were normal

at baseline and generally maintained through 24 weeks of treatment.

The mean (SD) Faecal Elastase-1 (a measure of exocrine pancreatic function) values at baseline and Week 24 are shown in Table 12, below.

Table 12: Efficacy Analyses, Full Analysis Set [Study 8 (ARRIVAL)]

Endpoint & Statistic	12 to less than 24 months		6 to less than 12 months		4 to less than 6 months		1 to less than 4 months	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Faecal Elastase-1 (µg/g)								
Baseline	19	182.2 (217.1)	10	119.6 (199.1)	5	184.0 (190.8)	6	344.8 (197.5)
Week 24 value	15	326.9 (152.1)	9	291.3 (170.5)	4	398.3 (117.5)	5	417.2 (185.1)
Absolute change from baseline at Week 24	15	164.7 (151.9)	9	159.3 (154.4)	4	181.0 (122.9)	5	103.4 (131.4)

Long Term Safety Study

In a 5-year observational safety surveillance study using real-world data from US and UK CF patient registries, key clinical outcomes were compared annually between ivacaftor-treated patients and untreated comparator patients matched on age, gender and disease severity as assessed by genotype. In the US registry there was a lower incidence of death, organ transplant, pulmonary exacerbations and hospitalisations in ivacaftor-treated versus untreated comparator patients. Results from the UK registry were similar.

In a disease progression analysis over the course of the study, a sub-set of patients with a record of continuous ivacaftor treatment (the majority of patients had the *G551D* mutation) had better preservation of lung function and improved BMI relative to untreated comparator patients.

Study 9 (VX17-770-128): Post-Marketing Observational Study

The use of ivacaftor in patients with CF who have ivacaftor-responsive *CFTR* mutations, based on *in vitro* FRT testing (see Section 5.1 PHARMACODYNAMIC PROPERTIES (Mechanism of action)) is supported with additional post-marketing observational data (Study 9). Study 9 was a 3-year observational study evaluating the real-world clinical response to ivacaftor in CF patients with mutations that are ivacaftor-responsive based on *in vitro* and/or clinical evidence. The data used in the analysis were collected by the United States Cystic Fibrosis Foundation Patient Registry (US CFFPR).

The study included data from 349 patients aged 2 years and older with selected FDA-approved ivacaftor-responsive *CFTR* mutations and a new record of ivacaftor initiation between 17 May 2017 and 31 December 2017. Analyses were performed using data for up to 36 months before and 36 months after initiation of ivacaftor treatment. Of the 349 patients in the ivacaftor cohort, 232 (66.5%) remained in the cohort at the beginning of the second year of follow-up, and 167 (47.9%) remained in the cohort at the beginning of the third year. The most common reason for cohort attrition was initiating use of another

CFTR modulator.

The study endpoints included lung function measurements ($ppFEV_1$), PEx, hospitalizations, nutritional parameters (weight, BMI, and z-scores for weight and BMI), death, organ transplantation, selected CF complications, and selected pulmonary pathogens. The results of the observational study support the effectiveness of ivacaftor in patients with CF with ivacaftor-responsive *CFTR* mutations.

Nineteen ivacaftor-responsive mutations were represented in the enrolled patient population. At ivacaftor initiation, the mean age of patients was 27.6 years and they had a mean $ppFEV_1$ of 77.5. The most common mutation subgroups were *D1152H* (21.2%), *A455E* (16.9%), *L206W* and *S945L* (11.7% each), *R347H* (9.2%), *P67L* (7.4%), and *R117C* (5.2%).

For each of the 12-month periods after ivacaftor initiation, in patients aged 6 years and older, $ppFEV_1$ was increased compared to the pre-treatment period. A subgroup analysis was performed in individual *CFTR* mutation subgroups where there were at least 5 patients with available $ppFEV_1$ data. There were 12 evaluable mutation subgroups and consistent $ppFEV_1$ increases were observed in all mutation sub-groups in the year after ivacaftor initiation. These improvements were generally maintained in the subsequent follow-up years.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of ivacaftor are similar between healthy adult volunteers and patients with CF. After oral administration of a single 150 mg dose to healthy volunteers in a fed state, the mean (±SD) for AUC and C_{max} were 10600 (5260) ng*hr/mL and 768 (233) ng/mL, respectively. The apparent terminal half-life was approximately 12 hours following asingle dose in the fed state. The apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and patients with CF. The mean (±SD) of CL/F for the 150 mg dose was 17.3 (8.4) L/hr in healthy subjects at steady state. After every 12-hour dosing, steady-state plasma concentrations of ivacaftor were reached by Days 3 to 5, with an accumulation ratioranging from 2.2 to 2.9.

Absorption

Following multiple oral dose administrations of ivacaftor, the exposure of ivacaftor generally increased with a dose from 25 mg every 12 hours to 450 mg every 12 hours. The exposure of ivacaftor increased approximately 2.5- to 4-fold when given with fat-containingfood. Therefore, ivacaftor should be administered with fat-containing food. The median t_{max} (range) is approximately 4.0 (3.0, 6.0) hours in the fed state.

Ivacaftor granules (2 x 75 mg sachets) had similar bioavailability to the 150 mg ivacaftor tablet when given with fat-containing food to adult patients. The effect of food on ivacaftorabsorption is similar for ivacaftor granules and the 150 mg tablet formulation.

Distribution

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells. After oral administration of 150 mg every 12 hours for 7 days in healthy volunteers in a fed state, themean (±SD) apparent volume of distribution was 353 (122) L.

Metabolism

Ivacaftor is extensively metabolised in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolised by CYP3A. M1 and M6 are the two major metabolites ofivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active.

Excretion

Following oral administration, the majority of ivacaftor (88%) was excreted in the faeces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately65% of the total dose excreted with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent and minimal urinary excretion (6.6%) of ivacaftor plus metabolites.

Special Populations

Children and Adolescents

Predicted ivacaftor exposure based on observed ivacaftor concentrations in Phase 2 and 3 studies as determined using population pharmacokinetic (PK) analysis is presented by age group (and body weight for patients less than 12 years of age) in Table 13. Exposures in 6-to 11-year-olds are predictions based on simulations from the population PK model using data obtained for this age group.

Table 13: Median and Mean (SD) Ivacaftor Exposure by Age Group

Age Group	Dose	$C_{min,\ ss}$ (ng/mL) (Median)	$C_{min,\ ss}$ (ng/mL) (Mean [SD])	AUC_{ss} (ng*h/mL) (Median)	AUC_{ss} (ng*h/mL) (Mean [SD])
1 month to less than 2 months (≥3 kg)*	13.4 mg q24h	242 †	300 (221)†	5140†	5840 (2980)†
2 months to less than 4 months (≥3 kg)*	13.4 mg q12h	342 †	406 (266)†	5710†	6450 (3430)†
4 months to less than 6 months (≥5 kg)*	25 mg q12h	300	371 (183)	5770	6480 (2520)
6 months to less than 12 months (5 kg to <7 kg)‡	25 mg q12h	336	336	5410	5410
6 months to less than 12 months (7 kg to <14 kg)	50 mg q12h	365	508 (252)	7600	9140 (4200)
12 months to less than 24 months (7 kg to <14 kg)	50 mg q12h	383	440 (212)	8900	9050 (3050)
12 months to less than 24 months (≥14 kg to <25 kg)	75 mg q12h	451	451 (125)	9600	9600 (1800)
2- to 5-year-olds (<14 kg)	50 mg q12h	536	577 (317)	9840	10500 (4260)
2- to 5-year-olds (≥14 kg to <25 kg)	75 mg q12h	580	629 (296)	10200	11300 (3820)
6- to 11-year-olds (≥14 kg to <25 kg)	75 mg q12h	584	641 (329)	10050	10760 (4470)
6- to 11-year-olds (≥25 kg)	150 mg q12h	838	958 (546)	13920	15300 (7340)
12- to 17-year-olds	150 mg q12h	508	564 (242)	8670	9240 (3420)
Adults (≥18 years old)	150 mg q12h	634	701 (317)	9840	10700 (4100)

* Patients 1 to less than 6 months of age were of ≥37 weeks gestational age.

† Exposures for 1 to less than 4 months of age are predictions based on simulations from the population PK model incorporating data from the given age group.

‡ Values based on data from a single patient; standard deviation not reported

Gender
The effect of gender on ivacaftor pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of ivacaftor. No dose adjustments are necessarybased on gender.

Renal Impairment
Pharmacokinetic studies have not been performed with ivacaftor in patients with renal impairment. In a human pharmacokinetic study, there was minimal elimination of ivacaftor andits metabolites in urine (only 6.6% of total radioactivity was recovered in the urine).

There was negligible urinary excretion of ivacaftor as unchanged parent (less than 0.01% following a single oral dose of 500 mg). Therefore, no dose adjustments are recommended formild and moderate renal impairment. However, caution is recommended when administering KALYDECO to patients with severe renal impairment (creatinine clearance less than or equalto 30 mL/min) or end-stage renal disease (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatic Impairment
Following a single dose of 150 mg of ivacaftor, adult patients with moderately impaired hepaticfunction (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max} (mean [±SD] of 735 [331] ng/mL), but an approximately 2-fold increase in ivacaftor $AUC_{0-\infty}$ (mean [±SD] of 16800[6140] ng*hr/mL) compared with healthy subjects matched for demographics.

Simulations for predicting the steady-state exposure of ivacaftor showed that by reducing the dosage from 150 mg q12h to 150 mg once daily, adults with moderate hepatic impairment would have comparable steady-state C_{min} values as those obtained with a dose of 150 mg q12h in adults without hepatic impairment. Therefore, a reduced dose of ivacaftor is recommended inpatients with moderate hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to6) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than 2-fold. Therefore, generally no dose adjustment is necessary for patients with mild hepatic impairment.

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15), but exposure is expected to be higher than in patients with moderate hepatic impairment. The use of KALYDECO in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such cases, the starting dose of ivacaftor should be reduced and dosing intervals should be modified according to clinical response and tolerability (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
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.

Carcinogenicity
Two-year oral studies in mice and rats to assess the carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 4- to 7-fold higher than the plasma levels measured in humans following ivacaftor therapy, and at least 1.2 to 2.4 times higher with respect to the summed AUC for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 16- to 29-fold higher than the plasma levels measured in humans following ivacaftor therapy,

and 6- to 9-fold higher with respect to the summed AUC for ivacaftor and its major metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

KALYDECO Tablets
Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate, croscarmellose sodium, sodium lauryl sulfate, silicon dioxide, magnesium stearate, carnauba wax, Opadry II complete film coating system 85F90614 Blue (PI# 108371), OPACODE monogramming ink S-1-17823 BLACK (PI# 12108).

KALYDECO Granules
Each sachet contains the following inactive ingredients: lactose monohydrate, hypromellose acetate succinate, croscarmellose sodium, sodium lauryl sulfate, silicon dioxide, magnesium stearate, mannitol, sucralose.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf-life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets (150 mg)
KALYDECO tablets are packaged in a thermoform (polychlorotrifluoroethylene [PCTFE]/foil) blister pack or a child-resistant high-density polyethylene (HDPE) bottle with a polypropylene, foil-lined induction seal closure and molecular sieve desiccant.

Tablet pack sizes:
Blister pack containing 56 film-coated tablets
Bottle containing 56 film-coated tablets

Granules (13.4 mg, 25 mg, 50 mg and 75 mg)
KALYDECO granules are packaged in a Biaxially Oriented Polyethylene Terephthalate/Polyethylene/Foil/Polyethylene (BOPET/PE/Foil/PE) sachet.

Granules pack sizes:
13.4 mg, 25 mg, 50 mg and 75 mg: pack size of 56 sachets (containing 4 individual wallets with 14 sachets per wallet).
13.4 mg: pack size of 28 sachets (containing 4 individual wallets with 7 sachets per wallet).

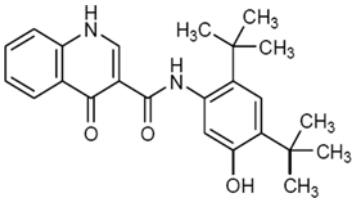
Not all KALYDECO pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



The empirical formula of ivacaftor is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. The pKa values of ivacaftor are 9.40 and 11.60. The log D value of ivacaftor is 5.68 at pH=7.4 and 25°C.

Ivacaftor is a white to off-white powder that is practically insoluble in water (<0.05 microgram/mL).

CAS number

873054-44-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

09 July 2013

10 DATE OF REVISION

04 November 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6 Fertility, Pregnancy and Lactation	Update to 'Use in Lactation' section to advise that published literature shows that ivacaftor is present in human milk

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