AUSTRALIAN PI – ORKAMBI® (LUMACAFTOR AND IVACAFTOR) TABLETS AND GRANULES

1 NAME OF THE MEDICINE

lumacaftor and ivacaftor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets
ORKAMBI 100/125 film-coated tablets contain 100 mg of lumacaftor and 125 mg of ivacaftor.
ORKAMBI 200/125 film-coated tablets contain 200 mg of lumacaftor and 125 mg of ivacaftor.

Granules
ORKAMBI 75/94 granules contain 75 mg lumacaftor and 94 mg ivacaftor per sachet.
ORKAMBI 100/125 granules contain 100 mg lumacaftor and 125 mg ivacaftor per sachet.
ORKAMBI 150/188 granules contain 150 mg lumacaftor and 188 mg ivacaftor per sachet.

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

3 PHARMACEUTICAL FORM

ORKAMBI 100/125 (lumacaftor/ivacaftor) film-coated tablets are supplied as pink, oval-shaped tablets. Each tablet is printed with “1V125” in black ink on one side and plain on the other.

ORKAMBI 200/125 (lumacaftor/ivacaftor) film-coated tablets are supplied as pink, oval-shaped tablets. Each tablet is printed with “2V125” in black ink on one side and plain on the other.

ORKAMBI (lumacaftor/ivacaftor) granules are supplied as white to off-white granules enclosed in unit dose sachets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ORKAMBI is indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

4.2 DOSE AND METHOD OF ADMINISTRATION

ORKAMBI should only be prescribed by physicians with experience in the treatment of CF. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the *F508del* mutation on both alleles of the *CFTR* gene.

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

Table 1: Recommended dose of ORKAMBI in patients aged 1 year and older

Age	Weight	Dose per unit (sachet/tablet)	ORKAMBI dose (every 12 hours)	
			Morning	Evening
1 to less than 2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg	1 sachet	1 sachet
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg		
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg		
2 through 5 years	<14 kg	lumacaftor 100 mg/ivacaftor 125 mg	1 sachet	1 sachet
2 through 5 years	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg	1 sachet	1 sachet
6 through 11 years	-	lumacaftor 100 mg/ivacaftor 125 mg	2 tablets	2 tablets
12 years and older	-	lumacaftor 200 mg/ivacaftor 125 mg	2 tablets	2 tablets

A fat-containing meal or snack should be consumed just before or just after dosing.

Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, chocolate, whole milk, whole-milk dairy products, breast milk, infant formula, meats, avocados, oily fish, and soy-based products (tofu) (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Film-coated 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. Some examples of soft foods or liquids include puréed fruits or vegetables, flavored yogurt or pudding, water, milk, breast milk, infant formula or juice. Food 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.

Use in Renal Insufficiency
No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using ORKAMBI in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in Hepatic Insufficiency
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A).
A dose reduction is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, after weighing the risks and benefits of treatment, ORKAMBI should be used with caution at a reduced dose (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

For dose adjustments for patients with hepatic impairment see Table 2.

Table 2: Dose adjustment recommendations in patients with hepatic impairment

Hepatic impairment	**Age (weight)**	**Dose adjustment**
Mild hepatic impairment (Child-Pugh Class A)	Patients aged 1 to less than 2 years (7 kg to <9 kg)	No dose adjustment
	Patients aged 1 to less than 2 years (9 kg to <14 kg)	
	Patients aged 1 to less than 2 years (≥14 kg)	
	Patients aged 2 through 5 years (<14 kg)	
	Patients aged 2 through 5 years (≥14 kg)	
	Patients aged 6 years and older	
Moderate hepatic impairment (Child-Pugh Class B)	Patients aged 1 to less than 2 years (7 kg to <9 kg)	**Day 1:** 1 sachet every morning and 1 sachet every evening. **Day 2:** 1 sachet every morning and skip the evening dose.
	Patients aged 1 to less than 2 years (9 kg to <14 kg)	
	Patients aged 1 to less than 2 years (≥14 kg)	
	Patients aged 2 through 5 years (<14 kg)	
	Patients aged 2 through 5 years (≥14 kg)	

	Patients aged 6 years and older	2 tablets every morning + 1 tablet every evening (12 hours later)
Severe hepatic impairment (Child-Pugh Class C)	Patients aged 1 to less than 2 years (7 kg to <9 kg)	1 sachet per day (or less frequently)
	Patients aged 1 to less than 2 years (9 kg to <14 kg)	
	Patients aged 1 to less than 2 years (≥14 kg)	
	Patients aged 2 through 5 years (<14 kg)	
	Patients aged 2 through 5 years (≥14 kg)	
	Patients aged 6 years and older	1 tablet every morning + 1 tablet every evening 12 hours apart (or less frequently)

Use in Patients with Advanced Lung Dysfunction
Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. In Study 809-106, patients aged 12 years and older with advanced lung disease ($ppFEV_1$ <40) initiated at a reduced dose (1 tablet every 12 hours for up to 2 weeks and subsequently increased to the full dose) experienced fewer respiratory events than patients initiated on the full dose. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in Combination with Strong CYP3A Inhibitors
No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking ORKAMBI. However, when initiating ORKAMBI in patients currently taking strong CYP3A inhibitors (e.g., itraconazole), reduce ORKAMBI dose to 1 tablet daily or 1 sachet every other day for the first week of treatment. Following this period, continue with the recommended daily dose.

If ORKAMBI is interrupted for more than 1-week and then re-initiated while taking strong CYP3A inhibitors, reduce ORKAMBI dose to 1 tablet daily or 1 sachet every other day for the first week of treatment re-initiation (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Following this period, continue with the recommended daily dose.

Use in Combination with Ciprofloxacin
No dose adjustment is required when ORKAMBI is used with ciprofloxacin.

4.3 CONTRAINDICATIONS

In cases of hypersensitivity to the active substance or to any component of this medication, patients should not be treated with this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with CF who are Heterozygous for the *F508del* Mutation in the *CFTR* Gene

ORKAMBI is not effective in patients with CF who have the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in the lack of CFTR production or that is not responsive to ivacaftor *in vitro*.

Patients with CF who have a Gating (Class III) Mutation in the *CFTR* Gene
ORKAMBI is not recommended for use in patients with CF who are heterozygous for the *F508del* mutation on one allele, with an ivacaftor-responsive mutation on the second allele, since the exposure of ivacaftor is very significantly reduced when dosed in combination with lumacaftor.

Use in Hepatic Impairment
Patients with advanced liver disease
Abnormalities in liver function, including advanced liver disease, can be present in patients with CF. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension receiving ORKAMBI. Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hepatobiliary Events
Elevated transaminases have been reported in patients with CF, including some receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Because an association with liver injury cannot be excluded, assessments of liver function tests (ALT, AST and bilirubin) are recommended before initiating ORKAMBI every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered.

In the event of significant elevation of ALT or AST, with or without elevated bilirubin [either ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN], dosing with ORKAMBI should be discontinued and laboratory tests closely followed until the abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The dose should be reduced in moderate or severe hepatic impairment; (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Use in Hepatic Insufficiency).

Respiratory Events
Respiratory events (e.g., chest discomfort, dyspnoea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with percent predicted FEV_1 ($ppFEV_1$) <40. Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy (see Section, 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and Section 5.1 PHARMACODYNAMIC PROPERTIES (Clinical Trials)). There is no experience of initiating treatment with ORKAMBI in patients having pulmonary exacerbations and this is not advisable.

Cardiovascular Effects
Effect on blood pressure
Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients during treatment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Decrease in heart rate
During the 24-week, placebo-controlled, Phase 3 studies, a maximum decrease in mean heart rate of 6

beats per minute (bpm) from baseline was observed on Day 1 and Day 15. After Week 4, the mean change in heart rate ranged from 1 to 2 bpm below baseline among patients treated with lumacaftor/ivacaftor. The percentage of patients with heart rate values <50 bpm on treatment was 11% for patients who received lumacaftor/ivacaftor, compared to 4.9% for patients who received placebo. Decreased in heart rate observed in clinical studies were not considered clinically relevant.

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

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

Patients after Organ Transplantation
ORKAMBI 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.

Interactions with Medicinal Products
Based on exposure and indicated doses, the drug interaction profile is considered to be the same for all dosage strengths and forms.

Substrates of CYP3A
Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products which are substrates of CYP3A, which may decrease their therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing effectiveness. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Strong CYP3A inducers
Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampicin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers (e.g., rifampicin, St. John's wort [*Hypericum perforatum*]) is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in Renal Impairment
Caution is recommended while using ORKAMBI 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- Use in Renal Insufficiency and Section 5.2 PHARMACOKINETIC PROPERTIES-Renal impairment).

Use in the Elderly
Clinical studies of ORKAMBI did not include patients aged 65 years and older. Thus, the efficacy and safety of ORKAMBI in elderly patients have not been evaluated.

Paediatric Use
The data to support use in 6-11 years included pivotal clinical studies in patients 12 years and older with a partial extrapolation to children (see Clinical Trials). Limited data is available in children aged less than 6 years of age.

Effects on Laboratory Tests
See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hepatobiliary Events.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lumacaftor is a strong inducer of CYP3A. Ivacaftor is a weak inhibitor of CYP3A when given as monotherapy. The net effect of lumacaftor/ivacaftor therapy is expected to be strong CYP3A induction.

Drug interaction studies were performed in adults with lumacaftor/ivacaftor and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies.

Effects of Other Medicines on Lumacaftor/Ivacaftor
CYP3A inhibitors
Co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. Due to the induction effect of lumacaftor on CYP3A, at steady-state, the net exposure of ivacaftor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours, the approved dose of ivacaftor monotherapy. Therefore, no dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking ORKAMBI.

However, when initiating ORKAMBI in patients currently taking strong CYP3A inhibitors, the dose should be reduced as per Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Use in Combination with Strong CYP3A Inhibitors.

Examples of strong CYP3A inhibitors include:
- ketoconazole, itraconazole, posaconazole, voriconazole
- telithromycin, clarithromycin.

No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.

CYP3A inducers
Co-administration of lumacaftor/ivacaftor with rifampicin, a strong CYP3A inducer, had minimal effect on the exposure of lumacaftor, but decreased ivacaftor exposure (AUC) by 57%. Therefore, co-administration of ORKAMBI is not recommended with strong CYP3A inducers such as:
- rifampicin, rifabutin
- phenobarbital, carbamazepine, and phenytoin
- St. John's wort (*Hypericum perforatum*).

No dose adjustment is recommended when used with moderate or weak CYP3A inducers.

Other recommendations
Ciprofloxacin
Co-administration of lumacaftor/ivacaftor with ciprofloxacin had minimal to mild effect on exposures of lumacaftor and ivacaftor. Therefore, no dose adjustment is required when ORKAMBI is used with ciprofloxacin.

Effects of Lumacaftor/Ivacaftor on Other Medicines

CYP3A and P-gp substrates

Lumacaftor is a strong inducer of CYP3A. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80%.

Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect of the medicinal product. Co-administration of ORKAMBI is not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index such as:

- midazolam, triazolam
- ciclosporin, everolimus, sirolimus, and tacrolimus.

Based on *in vitro* results which showed P-gp inhibition and pregnane-X-receptor (PXR) activation, lumacaftor has the potential to both inhibit and induce P-gp. Additionally, a clinical study with ivacaftor monotherapy showed that ivacaftor is a weak inhibitor of P-gp. Therefore, concomitant use of ORKAMBI with P-gp substrates may alter the exposure of these substrates. When co-administration with sensitive P-gp substrates such as digoxin is required, caution and appropriate monitoring are recommended.

CYP2B6 and CYP2C substrates

In vitro studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; however, inhibition of CYP2C8 and CYP2C9 has also been observed *in vitro*. Additionally, *in vitro* studies suggest that ivacaftor may inhibit CYP2C9. Therefore, concomitant use of ORKAMBI with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates. When co-administration is required, monitoring is recommended, such as the international normalised ratio with warfarin.

Established and other potentially significant drug interactions

Table 3 provides the established or predicted effect of lumacaftor/ivacaftor on other medicinal products or the effect of other medicinal products on lumacaftor/ivacaftor. The information reported in the Table 3 mostly derives from *in vitro* studies. The recommendations provided under "Clinical comment" in Table 3 are based on drug interaction studies, clinical relevance, or predicted interactions due to elimination pathways. Drug interactions that have the most clinical relevance are listed first.

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products

Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
Concomitant medicinal products of most clinical relevance		
Anti-allergics: montelukast	↔ LUM, IVA	No dose adjustment for montelukast is recommended. Appropriate clinical monitoring should be employed, as is reasonable, when co-administered with lumacaftor/ivacaftor.
	↓ montelukast Due to the induction of CYP3A/2C8/2C9 by LUM	Lumacaftor/ivacaftor may decrease the exposure of montelukast, which may reduce its efficacy.

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products		
Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
fexofenadine	↔ LUM, IVA	
	↑ or ↓ fexofenadine Due to potential induction or inhibition of P-gp	Dose adjustment of fexofenadine may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of fexofenadine.
Antibiotics: clarithromycin, telithromycin	↔ LUM ↑ IVA Due to inhibition of CYP3A by clarithromycin, telithromycin	No dose adjustment of lumacaftor/ivacaftor is recommended when clarithromycin or telithromycin are initiated in patients currently taking lumacaftor/ivacaftor.
	↓ clarithromycin, telithromycin Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one tablet daily or one sachet every other day for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking clarithromycin or telithromycin. An alternative to these antibiotics, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposures of clarithromycin and telithromycin, which may reduce their efficacy.
erythromycin	↔ LUM ↑ IVA Due to inhibition of CYP3A by erythromycin	No dose adjustment of lumacaftor/ivacaftor is recommended when co-administered with erythromycin.
	↓ erythromycin Due to induction of CYP3A by LUM	An alternative to erythromycin, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposure of erythromycin, which may reduce its efficacy.

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products		
Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↔ LUM ↓ IVA Due to induction of CYP3A by these anticonvulsants	
	↓ carbamazepine, phenobarbital, phenytoin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anticonvulsants is not recommended. The exposures of ivacaftor and the anticonvulsant may be significantly decreased, which may reduce the efficacy of both active substances.
Antifungals: itraconazole*, ketoconazole, posaconazole, voriconazole	↔ LUM ↑ IVA Due to inhibition of CYP3A by these antifungals	No dose adjustment of lumacaftor/ivacaftor is recommended when these antifungals are initiated in patients currently taking lumacaftor/ivacaftor.
	↓ itraconazole, ketoconazole, voriconazole Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one tablet daily or one sachet every other day for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking these antifungals.
	↓ posaconazole Due to induction of UGT by LUM	Concomitant use of lumacaftor/ivacaftor with these antifungals is not recommended. Patients should be monitored closely for breakthrough fungal infections if such drugs are necessary. Lumacaftor/ivacaftor may decrease the exposures of these antifungals, which may reduce their efficacy.

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products		
Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
fluconazole	↔ LUM ↑ IVA Due to inhibition of CYP3A by fluconazole	No dose adjustment of lumacaftor/ivacaftor is recommended when co-administered with fluconazole.
	↓ fluconazole Due to induction by LUM; fluconazole is cleared primarily by renal excretion as unchanged drug; however, modest reduction in fluconazole exposure has been observed with strong inducers	A higher dose of fluconazole may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of fluconazole, which may reduce its efficacy.
Anti-inflammatories: ibuprofen	↔ LUM, IVA	
	↓ ibuprofen Due to induction of CYP3A/2C8/2C9 by LUM	A higher dose of ibuprofen may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of ibuprofen, which may reduce its efficacy.
Anti-mycobacterials: rifabutin, rifampicin*, rifapentine	↔ LUM ↓ IVA Due to induction of CYP3A by anti-mycobacterials	
	↓ rifabutin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anti-mycobacterials is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor. A higher dose of rifabutin may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of rifabutin, which may reduce its efficacy.
	↔ rifampicin, rifapentine	

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products		
Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
Benzodiazepines: midazolam, triazolam	↔ LUM, IVA ↓ midazolam, triazolam Due to induction of CYP3A by LUM	 Concomitant use of lumacaftor/ivacaftor with these benzodiazepines is not recommended. Lumacaftor/ivacaftor will decrease the exposures of midazolam and triazolam, which will reduce their efficacy.
Hormonal contraceptives: ethinyl estradiol, norethindrone, and other progestogens	↓ ethinyl estradiol, norethindrone, and other progestogens Due to induction of CYP3A/UGT by LUM	Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor. Lumacaftor/ivacaftor may decrease the exposure of hormonal contraceptives, which may reduce their efficacy.
Immunosuppressants: ciclosporin, everolimus, sirolimus, tacrolimus (used after organ transplant)	↔ LUM, IVA ↓ ciclosporin, everolimus, sirolimus, tacrolimus Due to induction of CYP3A by LUM	 Concomitant use of lumacaftor/ivacaftor with these immunosuppressants is not recommended. Lumacaftor/ivacaftor will decrease the exposure of these immunosuppressants, which may reduce the efficacy of these immunosuppressants. The use of lumacaftor/ivacaftor in organ transplant patients has not been studied.
Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole	↔ LUM, IVA ↓ esomeprazole, lansoprazole, omeprazole Due to induction of CYP3A/2C19 by LUM	 A higher dose of these proton pump inhibitors may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of these proton pump inhibitors, which may reduce their efficacy.
Herbals: St. John's wort (*Hypericum perforatum*)	↔ LUM ↓ IVA Due to induction of CYP3A by St. John's wort	Concomitant use of lumacaftor/ivacaftor with St. John's wort is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor.

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products		
Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
Other concomitant medicinal products of clinical relevance		
Antiarrhythmics: digoxin	↔ LUM, IVA	
	↑ or ↓ digoxin Due to potential induction or inhibition of P-gp	The serum concentration of digoxin should be monitored and the dose should be titrated to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of digoxin.
Anticoagulants: dabigatran	↔ LUM, IVA	
	↑ or ↓ dabigatran Due to potential induction or inhibition of P-gp	Appropriate clinical monitoring should be employed when co-administered with lumacaftor/ivacaftor. Dose adjustment of dabigatran may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of dabigatran.
warfarin	↔ LUM, IVA	
	↑ or ↓ warfarin Due to potential induction or inhibition of CYP2C9 by LUM	The international normalised ratio (INR) should be monitored when warfarin co-administration with lumacaftor/ivacaftor is required. Lumacaftor/ivacaftor may alter the exposure of warfarin.
Antidepressants: citalopram, escitalopram, sertraline	↔ LUM, IVA	
	↓ citalopram, escitalopram, sertraline Due to induction of CYP3A/2C19 by LUM	A higher dose of these antidepressants may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of these antidepressants, which may reduce their efficacy.
bupropion	↔ LUM, IVA	
	↓ bupropion Due to induction of CYP2B6 by LUM	A higher dose of bupropion may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of bupropion, which may reduce its efficacy.

Table 3: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products		
Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
Corticosteroids, systemic: methylprednisolone, prednisone	↔ LUM, IVA ↓ methylprednisolone, prednisone Due to induction of CYP3A by LUM	A higher dose of these systemic corticosteroids may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of methylprednisolone and prednisone, which may reduce their efficacy.
H2 blockers: ranitidine	↔ LUM, IVA ↑ or ↓ ranitidine Due to potential induction or inhibition of P-gp	Dose adjustment of ranitidine may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of ranitidine.
Oral hypoglycemics: repaglinide	↔ LUM, IVA ↓ repaglinide Due to induction of CYP3A/2C8 by LUM	A higher dose of repaglinide may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of repaglinide, which may reduce its efficacy.
Note: ↑ = increase, ↓ = decrease, ↔ = no change; LUM = lumacaftor; IVA = ivacaftor. * Based on clinical drug-drug interaction studies. All other drug interactions shown are predicted.		

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Lumacaftor had no effects on fertility and reproductive performance indices in male and female rats at an oral dose of 1000 mg/kg/day [approximately 3 and 6.5 times, respectively, the maximum recommended human dose (MRHD) of the lumacaftor component of ORKAMBI on an AUC basis].

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding approximately 15 and 7 times, respectively, the systemic exposure anticipated in patients at the maximum recommended human dose (MRHD) of the ivacaftor component of ORKAMBI 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 8 and 5 times, respectively, the exposure at the MRHD of the ivacaftor component of ORKAMBI based on summed AUCs of ivacaftor and its metabolites).

Use in Pregnancy
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.

No adequate and well-controlled studies of ORKAMBI in pregnant women have been conducted. Adverse effects on embryofetal development have been observed in studies in animals, conducted with the individual active components. Lumacaftor, ivacaftor, and/or their metabolites were shown to cross the placenta in rats and rabbits.

Lumacaftor produced no teratogenicity or other adverse effects on embryofetal development in rats receiving oral doses up to 2000 mg/kg/day (yielding 8 times the plasma AUC for lumacaftor in patients at the maximum recommended dose) or in rabbits at up to 100 mg/kg/day (relative exposure based on AUC, 3). At 200 mg/kg/day, treatment with lumacaftor was associated with abortions and a slight increase in the incidence of minor skeletal abnormalities in rabbits (relative exposure based on AUC, 5). This occurred in conjunction with significant maternal toxicity, and the findings are not considered to reflect a direct effect of lumacaftor on the developing fetus.

Developmental toxicity studies with ivacaftor revealed no teratogenicity in rats at oral doses up to 200 mg/kg/day (yielding 7 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, ≥4). 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.

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

Use in Lactation
It is unknown whether lumacaftor and/or ivacaftor and metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of both lumacaftor and ivacaftor into the milk of lactating female rats. As such, risks to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from lumacaftor/ivacaftor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ORKAMBI is not expected to have an impact on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Trials
The safety profile of ORKAMBI is based primarily on the pooled data from 1108 patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene and who received at least 1 dose of study drug in two double-blind, placebo-controlled, Phase 3 clinical studies, each with 24 weeks of treatment [Study 809-103 (TRAFFIC) and Study 809-104 (TRANSPORT)]. A total of 738 patients received lumacaftor/ivacaftor (369 patients received lumacaftor 400 mg q12h in combination with ivacaftor 250 mg q12h and 369 patients received lumacaftor 600 mg qd in combination with ivacaftor 250 mg q12h) and 370 patients received placebo. Of the 1108 patients, 49% were female and 99% were Caucasian.

The proportion of patients who prematurely discontinued study drug due to adverse events was 4.2% for lumacaftor/ivacaftor-treated patients and 1.6% for placebo-treated patients. The only adverse

events which resulted in discontinuation in at least 0.5% of patients receiving lumacaftor/ivacaftor were increased blood creatine phosphokinase (0.5%) and hepatobiliary events (0.5%).

The most common adverse effects reactions experienced by patients who received lumacaftor/ivacaftor in the pooled, placebo-controlled, Phase 3 studies were dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo).

The only serious adverse reactions occurring in at least 0.5% of patients on lumacaftor/ivacaftor and greater than placebo were hepatobiliary events, including 4 reported as transaminase elevations, 2 as cholestatic hepatitis, and 1 as hepatic encephalopathy.

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

Table 4. Adverse events with an incidence of at least 10% in any treatment group of patients aged 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene

	ORKAMBI Total	**Placebo**
Adverse reaction Preferred term	**N=738**	**N=370**
Infective pulmonary exacerbation of cystic fibrosis	277 (37.5)	182 (49.2)
Cough	225 (30.5)	148 (40.0)
Headache	116 (15.7)	58 (15.7)
Sputum increased	109 (14.8)	70 (18.9)
Dyspnoea	103 (14.0)	29 (7.8)
Haemoptysis	102 (13.8)	50 (13.5)
Diarrhoea	81 (11.0)	31 (8.4)
Nausea	75 (10.2)	28 (7.6)
Nasopharyngitis	71 (9.6)	40 (10.8)
Nasal congestion	57 (7.7)	44 (11.9)

Tabulated List of Adverse Reactions

Adverse reactions identified in patients aged 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene are presented in Table 5 and are 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 ORKAMBI-treated patients

System organ class	**Frequency category**	**Adverse effects (Preferred term)**
Infections and infestations	common	Rhinitis, Upper respiratory tract infection
Vascular disorders	uncommon	Hypertension
Nervous system disorders	very common	Headache
	uncommon	Hepatic encephalopathy[†]
Respiratory, thoracic and mediastinal	very common	Nasal congestion, Dyspnoea, Productive cough, Sputum increased

disorders	common	Respiration abnormal, Oropharyngeal pain, Rhinorrhoea
Gastrointestinal disorders	very common	Diarrhoea, Nausea, Abdominal pain upper
	common	Flatulence, Vomiting
Hepatobiliary disorders	common	Transaminase elevations
	uncommon	Cholestatic hepatitis‡
Skin and subcutaneous tissue disorders	common	Rash
Reproductive system and breast disorders	common	Dysmenorrhoea, Menstruation irregular, Metrorrhagia
	uncommon	Amenorrhoea, Menorrhagia, Oligomenorrhoea, Polymenorrhoea
Investigations	uncommon	Blood pressure increased

† 1 patient out of 738

‡ 2 patients out of 738

Safety data from a 96-week rollover extension study [Study 809-105(PROGRESS)] in 1029 patients aged 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene, were consistent with in Studies 809-103 (TRAFFIC) and 809-104 (TRANSPORT) (see Section 5.1 PHARMACODYNAMIC PROPERTIES). The respiratory events in treatment naïve patients who were initiated on ORKAMBI in Study 809-105 (PROGRESS) were comparable to those who were initiated on ORKAMBI in preceding Studies 809-103 (TRAFFIC) and 809-104 (TRANSPORT).

Studies in patients aged 6 through 11 years
The safety profile observed in studies in patients 6-11 years old [Study 809-109 and 809-011 (Part B)] was similar to that observed in Studies 809-103 (TRAFFIC) and 809-104 (TRANSPORT).

Adverse reactions that are not listed in Table 5, and that occurred in ≥5% of lumacaftor/ivacaftor- treated patients with an incidence of ≥3% higher than placebo (Study 809-11(Part B) included: productive cough (17.5% vs. 5.9%), nasal congestion (16.5% vs. 7.9%), headache (12.6% vs. 8.9%), abdominal pain upper (12.6% vs. 6.9%), and sputum increased (10.7% vs. 2.0%).

Safety data from a 96-week rollover extension study in 239 patients aged 6 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene (Study 809-110) were generally consistent with Studies 809-109 and 809-011 (Part B) (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Studies in patients aged 2 through 5 years
In a 24-week, open-label, multicenter Phase 3 study in 60 patients aged 2 through 5 years with CF who are homozygous for the *F508del-CFTR* mutation (Study 809-115) the safety profile was generally consistent to that observed in studies in patients aged 6 years and older (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Safety data from a 96-week rollover extension study in 57 patients aged 2 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene (Study 809-116) were generally consistent with Study 809-115 and patients aged 6 years and older (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Studies in patients aged 1 to less than 2 years

The safety profile from a 24-week, open-label, multicenter Phase 3 study in 46 patients aged 1 to less than 2 years with CF who are homozygous for the *F508del-CFTR* mutation (Study 809-122) was generally consistent with the established safety profile of lumacaftor/ivacaftor observed in patients aged 2 years and older.

Safety data were obtained from a 96-week open-label clinical study (Study 809-124) in 52 patients aged 1 year and older (39 rolled over from Study 809-122 and 13 ORKAMBI naïve patients). The safety profile was similar to that observed in Study 809-122.

Detailed description of Selected Adverse Reactions

Hepatobiliary events
Patients over 12 years of age
During the 24-week, placebo-controlled, Phase 3 studies (Studies 809-103 (TRAFFIC) and 809-104 (TRANSPORT), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 0.8%, 2.0%, and 5.2% in the patients receiving lumacaftor/ivacaftor, and 0.5%, 1.9%, and 5.1% in the placebo-treated patients. The incidence of transaminase-related adverse drug reactions was 5.1% and 4.6% in lumacaftor/ivacaftor-treated patients and those who received placebo, respectively. Seven patients who received lumacaftor/ivacaftor had liver-related serious adverse events with elevated transaminases, including 3 with concurrent elevation in total bilirubin. Following discontinuation of lumacaftor/ivacaftor, liver function tests returned to baseline or improved substantially in all patients. While alternative etiologies were present, the potential for liver injury associated with lumacaftor/ivacaftor cannot be excluded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Among seven patients with pre-existing cirrhosis and/or portal hypertension who received lumacaftor/ivacaftor in the placebo-controlled Phase 3 studies, worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy was observed in one patient. The event occurred within 5 days of the start of dosing and resolved following discontinuation of lumacaftor/ivacaftor (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients aged 6 through 11 years
Abnormal transaminases were more commonly observed in children.
During the 24-week, open-label Phase 3 clinical study in 58 patients aged 6 through 11 years (Study 809-011 (Part B)), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 5.3%, 8.8%, and 19.3%. No patients had an increase in total bilirubin levels >2 x ULN. Lumacaftor/ivacaftor dosing was maintained or successfully resumed after interruption in all patients with transaminase elevations, except 1 patient who discontinued treatment.

During the 24-week, placebo-controlled Phase 3 clinical study in 204 patients aged 6 through 11 years (Study 809-109), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 1.0%, 4.9%, and 12.6% in the lumacaftor/ivacaftor patients, and 2.0%, 3.0%, and 7.9% in the placebo-treated patients. No patients had total bilirubin levels >2 x ULN. Two patients in the lumacaftor/ivacaftor group and two patients in the placebo group discontinued treatment due to transaminase elevations.

Patients aged 2 through 5 years
During the 24-week, open-label Phase 3 clinical study in 60 patients aged 2 through 5 years (Study 809-115), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 8.3% (5/60), 11.7% (7/60), and 15.0% (9/60). No patients had total bilirubin levels >2 x ULN. Three patients discontinued lumacaftor/ivacaftor treatment due to transaminase elevations.

Patients aged 1 to less than 2 years
During the 24-week, open-label Phase 3 clinical study in 46 patients aged 1 to less than 2 years (Study 809-122), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 2.2% (1/46),

4.3% (2/46), and 10.9% (5/46), respectively. No patients had total bilirubin levels >2 x ULN. One patient discontinued lumacaftor/ivacaftor treatment due to transaminase elevations.

Respiratory events
Patients over 12 years of age
During the 24-week, placebo-controlled, Phase 3 studies [Studies 809-103 (TRAFFIC) and 809-104 (TRANSPORT)], incidence of respiratory adverse reactions (e.g., chest discomfort, dyspnoea, and respiration abnormal such as respiratory chest tightness) was 26.3% in lumacaftor/ivacaftor-treated patients compared to 17.0% in patients who received placebo. The incidence of these events were more common in patients treated with lumacaftor/ivacaftor with lower pre-treatment FEV_1. Approximately three-quarters of the events began during the first week of treatment, and in most patients the events resolved without dosing interruption. The majority of events were mild or moderate in severity, non-serious, and did not result in treatment discontinuation.

During a 24-week, open-label, Phase 3b clinical study (Study 809-106) in 46 patients aged 12 years and older with advanced lung disease ($ppFEV_1$ <40) [mean $ppFEV_1$ 29.1 at baseline (range: 18.3 to 42.0)], the incidence of respiratory events was 65.2%. In the subgroup of 28 patients who were initiated at the full dose of lumacaftor/ivacaftor (2 tablets every 12 hours), the incidence was 71.4%, and in the 18 patients who were initiated at a reduced dose of lumacaftor/ivacaftor (1 tablet every 12 hours for up to 2 weeks, and subsequently increased to the full dose), the incidence was 55.6%. Of the patients who were initiated lumacaftor/ivacaftor at the full dose, one patient had a serious respiratory event, three patients subsequently had their dose reduced, and three patients discontinued treatment. No serious respiratory events, dose reductions or discontinuations were seen in patients who were initiated at the half dose (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients aged 6 through 11 years
During the 24-week, open-label Phase 3 clinical study (Study 809-011 (Part B)) in 58 patients aged 6 through 11 years (mean baseline $ppFEV_1$ was 91.4), the incidence of respiratory adverse reactions was 6.9% (4/58).

During the 24-week, placebo-controlled Phase 3 clinical study (Study 809-109) in patients aged 6 through 11 years (mean baseline $ppFEV_1$ was 89.8), the incidence of respiratory adverse reactions was 18.4% in lumacaftor/ivacaftor patients and 12.9% in placebo patients. A decline in $ppFEV_1$ at initiation of therapy was observed during serial post-dose spirometry assessments. The absolute change from pre-dose at 4-6 hours post-dose was -7.7 on Day 1 and -1.3 on Day 15 in lumacaftor/ivacaftor patients. The post-dose decline was resolved by Week 16.

Menstrual abnormalities
During the 24-week, placebo-controlled, Phase 3 studies, the incidence of combined menstrual abnormality events (amenorrhoea, dysmenorrhoea, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhoea, and polymenorrhoea) was 9.9% in lumacaftor/ivacaftor-treated female patients and 1.7% in placebo-treated females. These menstrual events occurred more frequently in the subset of female patients who were taking hormonal contraceptives (25.0%) compared to patients who were not taking hormonal contraceptives (3.5%) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Most of these reactions were mild or moderate in severity and non-serious.

Increased blood pressure
During the 24-week, placebo-controlled, Phase 3 studies [Study 809-103 (TRAFFIC) and 809-104 (TRANSPORT)], adverse reactions related to increased blood pressure (e.g., hypertension, blood pressure increased) were reported in 0.9% (7/738) of patients treated with lumacaftor/ivacaftor and in no patients who received placebo.

In patients treated with lumacaftor/ivacaftor the maximum increase from baseline (114 mm Hg systolic and 69 mm Hg diastolic) in mean systolic and diastolic blood pressure was 3.1 mm Hg and

1.8 mm Hg, respectively. In patients who received placebo the maximum increase from baseline (114 mm Hg systolic and 69 mm Hg diastolic) in mean systolic and diastolic blood pressure was 0.9 mm Hg and 0.9 mm Hg, respectively.

The proportion of patients who experienced a systolic blood pressure value >140 mm Hg or a diastolic blood pressure >90 mm Hg on at least two occasions was 3.4% and 1.5% in patients treated with lumacaftor/ivacaftor, respectively, compared with 1.6% and 0.5% in patients who received placebo (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of ORKAMBI. 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

Hepatic impairment: Post-marketing cases of liver function decompensation including liver failure leading to death have been reported in CF patients with pre-existing cirrhosis with portal hypertension who were treated with lumacaftor/ivacaftor (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Respiratory events: Post-marketing reports of respiratory events were more common in patients with lower ppFEV$_1$. Some of these events were serious and led to lumacaftor/ivacaftor treatment discontinuation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune system disorders: Anaphylaxis.

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).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The *F508del* mutation impacts the CFTR protein in multiple ways, primarily by causing a defect in cellular processing and trafficking that reduces the quantity of CFTR at the cell surface. The small amount of *F508del-CFTR* that reaches the cell surface has low channel open probability (defective channel gating). Lumacaftor is a CFTR corrector that acts directly on *F508del-CFTR* to improve its cellular processing and trafficking, thereby increasing the quantity of functional CFTR at the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of lumacaftor and ivacaftor is increased quantity and function of *F508del-CFTR* at the cell surface,

resulting in increased chloride ion transport.

Effects on sweat chloride
Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24-week, open-label Phase 3 clinical study [Study 809-011(Part B)] and as part of a 24-week, placebo- controlled Phase 3 clinical study (Study 809-109) in patients with CF, aged 6 through 11 years old who were homozygous for the *F508del* mutation in the *CFTR* gene. There was no direct correlation between the decrease in sweat chloride levels and improvement in lung function.

In Study 809-011 (Part B), treatment with lumacaftor/ivacaftor lumacaftor 200 mg/ivacaftor 250 mg q12h for 24 weeks, demonstrated a reduction in sweat chloride as early as Day 15 that was sustained through Week 24. The within-group least square (LS) mean absolute change from baseline in sweat chloride was -20.4 mmol/L (95% CI: -23.9, -16.9; *P*<0.0001) at Day 15 and -24.8 mmol/L (95% CI: -29.1, -20.5; *P*<0.0001) at Week 24. In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The within-group LS mean absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 21.3 mmol/L (95% CI: 18.6, 24.0; *P*<0.0001). This change represents a return to baseline after treatment washout.
In Study 809-109, treatment with lumacaftor 200 mg/ivacaftor 250 mg q12h for 24 weeks demonstrated a decrease in sweat chloride compared to placebo that was sustained through 24 weeks of treatment. The treatment difference (LS mean) in sweat chloride for the average absolute change at Day 15 and at Week 4 as compared to placebo was -20.8 mmol/L (95% CI: -23.4, -18.2). The treatment difference (LS mean) in sweat chloride for the absolute change at Week 24 as compared to placebo was -24.9 mmol/L).

Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24-week, open-label Phase 3 clinical study (Study 809-115) in 60 patients with CF, aged 2 through 5 years (homozygous for *F508del*) who received either lumacaftor 100 mg/ivacaftor 125 mg every 12 hours or lumacaftor 150 mg/ivacaftor 188 mg every 12 hours for 24 weeks. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week 4 through Week 24. The mean absolute change from baseline in sweat chloride was –31.7 mmol/L (95% CI: -35.7, -27.6; *P*<0.0001) at Week 24. In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The mean absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was an increase of 33.0 mmol/L (95% CI: 28.9, 37.1; *P*<0.0001). This change represents a return to baseline after treatment washout.

Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24-week, open-label Phase 3 clinical study (Study 809-122) in 46 patients with CF, aged 1 to less than 2 years (homozygous for *F508del*) who received lumacaftor 75 mg/ivacaftor 94 mg (patient weighing 7 kg to <9 kg at screening), lumacaftor 100 mg/ivacaftor 125 mg (patient weighing 9 kg to <14 kg at screening), lumacaftor 150 mg/ivacaftor 188 mg (patient weighing ≥14 kg at screening), every 12 hours for 24 weeks. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week 4 which was sustained through Week 24. The mean absolute change from baseline in sweat chloride at Week 24 was -29.1 (13.5) mmol/L (95% CI: -34.8, -23.4). In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The mean (SD) absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 27.3 (11.1) mmol/L (95% CI: 22.3, 32.3). This change represents a return towards baseline after treatment washout.

Clinical Trials

Studies 809-103 (TRAFFIC) and 809-104 (TRANSPORT) in patients with CF who are homozygous for the F508del mutation in the CFTR *gene*

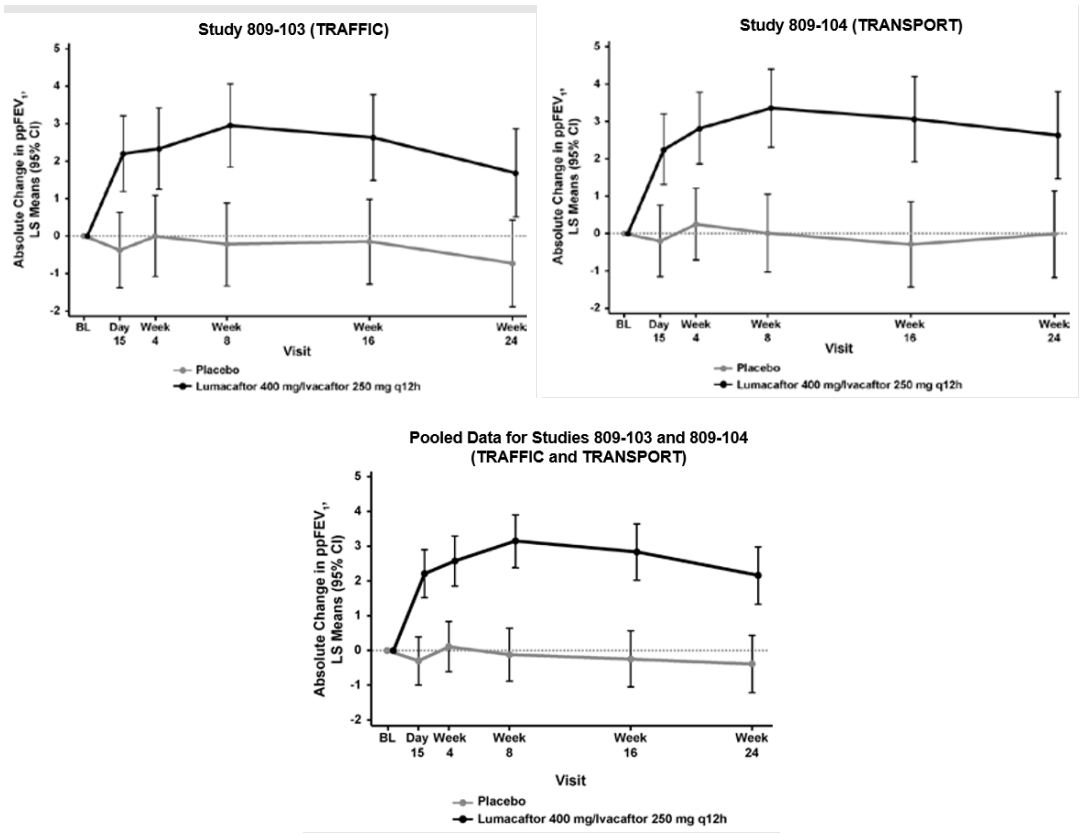
The efficacy of ORKAMBI in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomised, double-blind, placebo-controlled clinical trials of 1108 clinically stable patients with CF, in which 737 patients were randomised to and dosed with lumacaftor/ivacaftor. Patients in both trials were randomised 1:1:1 to receive lumacaftor 600 mg once daily/ivacaftor 250 mg q12h; lumacaftor 400 mg q12h/ivacaftor 250 mg q12h; or placebo. Patients took the study drug with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline). Patients from these trials were eligible to roll over into a blinded extension study.

Study 809-103 (TRAFFIC) evaluated 549 patients with CF who were aged 12 years and older (mean age 25.1 years) with percent predicted FEV_1 ($ppFEV_1$) at screening between 40-90 [mean $ppFEV_1$ 60.7 at baseline (range: 31.1 to 94.0)]. **Study 809-104 (TRANSPORT)** evaluated 559 patients aged 12 years and older (mean age 25.0 years) with $ppFEV_1$ at screening between 40-90 [mean $ppFEV_1$ 60.5 at baseline (range: 31.3 to 99.8)]. Patients with a history of colonisation with organisms associated with a more rapid decline in pulmonary status such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 3 or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 times the ULN or total bilirubin ≥2 times the ULN) were excluded.

The primary efficacy endpoint in both studies was the absolute change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. Other efficacy variables included relative change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24; absolute change from baseline in BMI at Week 24; absolute change from baseline in CFQ-R Respiratory Domain at Week 24; the proportion of patients achieving ≥5% relative change from baseline in $ppFEV_1$ using the average of Week 16 and Week 24; and number of pulmonary exacerbations (including those requiring hospitalisation or IV antibiotic therapy) through Week 24.

In both studies, treatment with ORKAMBI resulted in a statistically significant improvement in $ppFEV_1$ (Table 6). The treatment difference between lumacaftor/ivacaftor 400 mg/250 mg q12h and placebo for the mean absolute change (95% CI) in $ppFEV_1$ from baseline at Week 24 (assessed as the average of the treatment effects at Week 16 and at Week 24) was 2.6 percentage points (1.2, 4.0) in Study 809-103 (TRAFFIC)(P=0.0003) and 3.0 percentage points (1.6, 4.4) in Study 809-104 (TRANSPORT) (P<0.0001). Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained throughout the 24-week treatment period (Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, disease severity, sex, and geographic region. The Phase 3 trials of lumacaftor/ivacaftor included 81 patients with $ppFEV_1$ <40 at baseline (including 29 who received lumacaftor 400 mg/ivacaftor 250 mg q12h). The treatment difference in this subgroup was comparable to that observed in patients with $ppFEV_1$ ≥40. See Table 6 for a summary of primary and key secondary outcomes in Studies 809-103 and 809-104.

Figure 1. Absolute change from baseline at each visit in percent predicted FEV_1 in Study 809-103 (TRAFFIC), Study 109-104 (TRANSPORT), and Pooled Data for Studies 809-103 and 809-104 (TRAFFIC and TRANSPORT).



LS: least squares; q12h: every 12 hours.

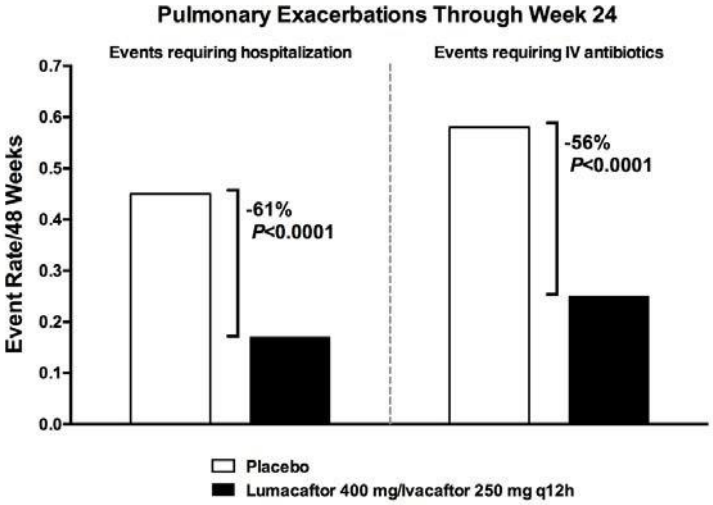
Table 6: Summary of primary and key secondary outcomes in Study 809-103 (TRAFFIC) and Study 809-104 (TRANSPORT)*

		Study 809-103 (TRAFFIC)		Study 809-104 (TRANSPORT)		Pooled Study 809-103 (TRAFFIC) and Study 809-104 (TRANSPORT)	
		Placebo (n=184)	LUM 400 mg/IVA 250 mg q12h (n=182)	Placebo (n=187)	LUM 400 mg/IVA 250 mg q12h (n=187)	Placebo (n=371)	LUM 400 mg/IVA 250 mg q12h (n=369)
Absolute change in ppFEV$_1$ at Week 24† (percentage points)	Treatment difference	–	2.6 (*P*=0.0003)‡	–	3.0 (*P*<0.0001)‡	–	2.8 (*P*<0.0001
	Within-group change	-0.44 (*P*=0.4002)	2.2 (*P*<0.0001)	-0.15 (*P*=0.7744)	2.9 (*P*<0.0001)	-0.32 (*P*<0.3983)	2.5 (*P*<0.0001
Relative change in ppFEV$_1$ at Week 24† (%)	Treatment difference	–	4.3 (*P*=0.0006)‡	–	5.3 (*P*<0.0001)‡	–	4.8 (*P*<0.0001
	Within-group change	-0.34 (*P*=0.7113)	4.0 (*P*<0.0001)	0 (*P*=0.9983)	5.3 (*P*<0.0001)	-0.17 (*P*=0.8030)	4.6 (*P*<0.0001
Absolute change in BMI at Week 24 (kg/m^2)	Treatment difference	–	0.13 (*P*=0.1938)	–	0.36 (*P*<0.0001)‡	–	0.24 (*P*=0.0004)
	Within-group change	0.19 (*P*=0.0065)	0.32 (*P*<0.0001)	0.07 (*P*=0.2892)	0.43 (*P*<0.0001)	0.13 (*P*=0.0066)	0.37 (*P*<0.0001)
Absolute change in CFQ-R Respiratory Domain Score at Week 24 (points)	Treatment difference	–	1.5 (*P*=0.3569)	–	2.9 (*P*=0.0736)	–	2.2 (*P*=0.0512
	Within-group change	1.1 (*P*=0.3423)	2.6 (*P*=0.0295)	2.8 (*P*=0.0152)	5.7 (*P*<0.0001)	1.9 (*P*=0.0213)	4.1 (*P*<0.0001
Proportion of patients with ≥5% relative change in ppFEV$_1$ using the average o Week 16 and Week 24	%	22%	37%	23%	41%	22%	39%
	Odds ratio	–	2.06 (*P*=0.0023)	–	2.38 (*P*=0.0001)	–	2.22 (*P*<0.0001)
Number of pulmonary exacerbations through Week 24	# of events (rate per 48 weeks)	112 (1.07)	73 (0.71)	139 (1.18)	79 (0.67)	251 (1.14)	152 (0.70)
	Rate ratio	–	0.66 (*P*=0.0169)	–	0.57 (*P*=0.0002)	–	0.61 (*P*<0.0001)

* In each study, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs. placebo; at each step, $P \leq 0.0250$ and all previous tests also meeting this level of significance were required for statistical significance.
† As assessed as the average of the treatment effects at Week 16 and Week 24.
‡ Indicates statistical significance confirmed in the hierarchical testing procedure.

At Week 24, the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with ORKAMBI compared with placebo. In the pooled analysis, the rate ratio of exacerbations through Week 24 in subjects treated with lumacaftor 400 mg/ivacaftor 250 mg q12h (n=369) was 0.61 (P<0.0001), representing a reduction relative to placebo of 39%. The event rate per year, annualised to 48 weeks, was 0.70 in the active group and 1.14 in the placebo group. Treatment with ORKAMBI significantly decreased the risk for exacerbations requiring hospitalisation vs. placebo by 61% (rate ratio=0.39, P<0.0001; event rate per 48 weeks was 0.17 for active and 0.45 for placebo) and reduced exacerbations requiring treatment with intravenous antibiotics by 56% (rate ratio=0.44, P<0.0001; event rate per 48 weeks 0.25 for active and 0.58 for placebo). See Figure 2.

Figure 2. Pulmonary Exacerbations through Week 24



Study 809-102, Cohort 4: Patients with CF who are heterozygous for the F508del mutation in the CFTR *gene*

Study 809-102 was a multicenter, double–blind, randomised, placebo–controlled, Phase 2 trial in 125 patients with CF aged 18 years and older who had a $ppFEV_1$ of 40 to 90, inclusive. All patients were tested for the CF genotype at screening; eligible patients had the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in the lack of CFTR production or a CFTR that is not responsive to ivacaftor *in vitro*.

Patients received either ORKAMBI (n=62) or placebo (n=63) q12h in addition to their prescribed CF therapies. The median age of patients enrolled was 28 years and the mean baseline $ppFEV_1$ was 61.47. Patients with a history of colonisation with organisms such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 times the ULN or total bilirubin ≥2 times the ULN) were excluded.

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline at Day 56 in $ppFEV_1$. Treatment with ORKAMBI resulted in no significant improvement in $ppFEV_1$ relative to placebo in patients with CF heterozygous for the *F508del* mutation in the *CFTR* gene [treatment difference 0.60 (*P*=0.5978)]. There were no meaningful differences between patients treated with ORKAMBI compared to placebo for the following secondary endpoints: relative change in $ppFEV_1$, BMI, and weight; however, there was a nominally statistically significant change in the CF respiratory symptom score.

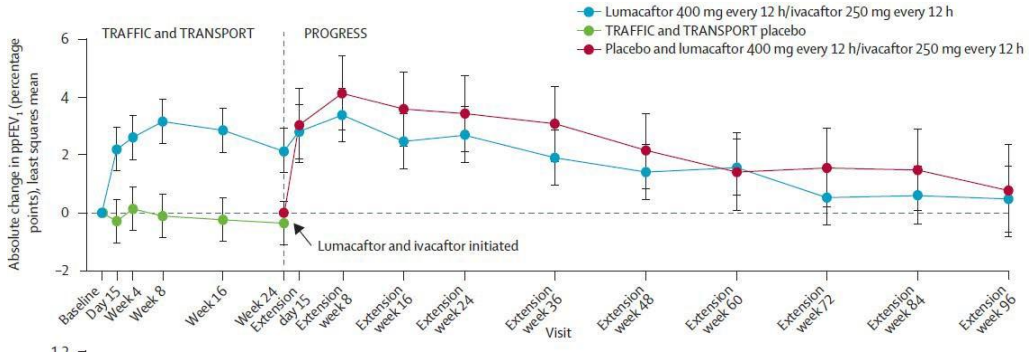
Study 809-105: Long-term safety and efficacy rollover trial

Study 809-105 (PROGRESS), a Phase 3, parallel-group, multicenter, rollover extension study was conducted in patients with CF aged 12 years and older, that included patients from Study 809-103 1 (TRAFFIC) and Study 809-104 (TRANSPORT). This 96-week extension study was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 1108 patients who received any treatment in Study 809-103 1 (TRAFFIC) or Study 809-104 (TRANSPORT), 1029 patients (93%) were dosed and received active treatment in Study 809-105 (PROGRESS) for up to an additional 96 weeks (i.e., up to a total of 120 weeks). A total of 82% (421 of 516 eligible patients) completed 72 weeks of this study; 42% completed 96 weeks. Majority of patients discontinued for reasons

other than safety. The efficacy analysis of this extension study included data up to Week 72 with a sensitivity analysis that included data up to Week 96.

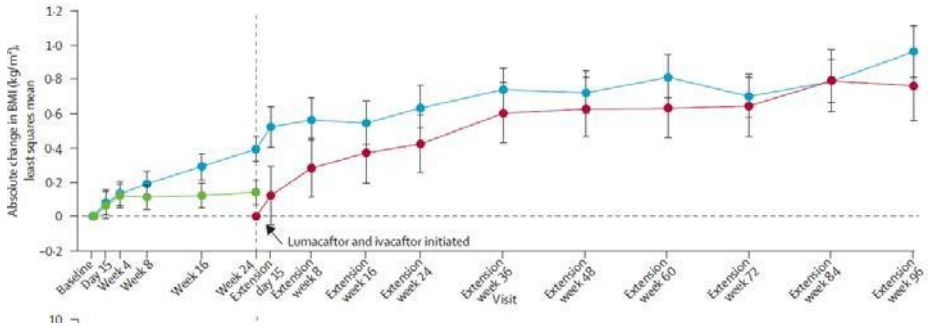
The absolute change in $ppFEV_1$ observed in patients treated with ORKAMBI in Study 809-103 (TRAFFIC) or Study 809-104 (TRANSPORT) remained above baseline at Week 72 (LS mean 0.5, 95% CI -0.4 to 1.5). In patients who transitioned from placebo to ORKAMBI, an improvement in $ppFEV_1$ was observed on initiation of active treatment which was maintained above baseline through Week 72 (LS mean change 1.5, 95% CI 0.2 to 2.9). At Week 96 the LS mean change in $ppFEV_1$ for patients continuing ORKAMBI was 0.5, 95% CI -0.7 to 1.6 and for patients transitioning from placebo to ORKAMBI was 0.8, 95% CI -0.8 to 2.3 (Figure 3).

Figure 3. Absolute change from baseline in percent predicted FEV_1 at each visit



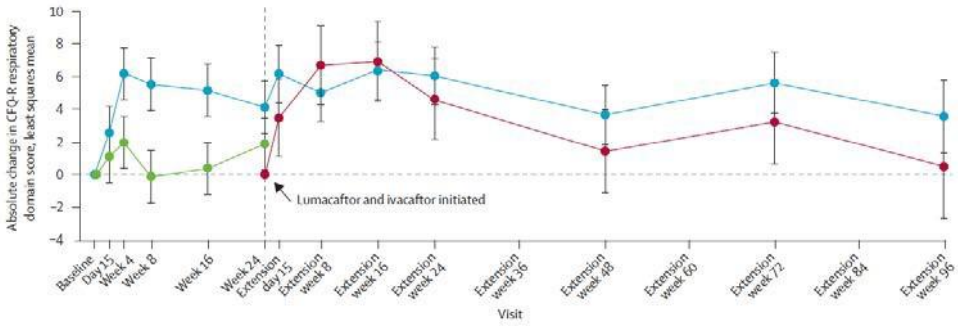
Patients treated with ORKAMBI for 24 weeks in Study 809-103 (TRAFFIC) or Study 809-104 (TRANSPORT) continued to show improvement in BMI through Study 809-105 (PROGRESS). At baseline the BMI (SD) was 21.5 kg/m^2 (3.0). At Week 72, the LS mean of absolute change from baseline was 0.69 (95% CI 0.56-0.81) in patients who remained on ORKAMBI and in patients who transitioned to ORKAMBI, was 0.62 (95% CI 0.45-0.79). Similar improvement in BMI was observed up to Week 96 in both treatment groups (Figure 4).

Figure 4. Absolute change from baseline in BMI (kg/m^2) at each visit



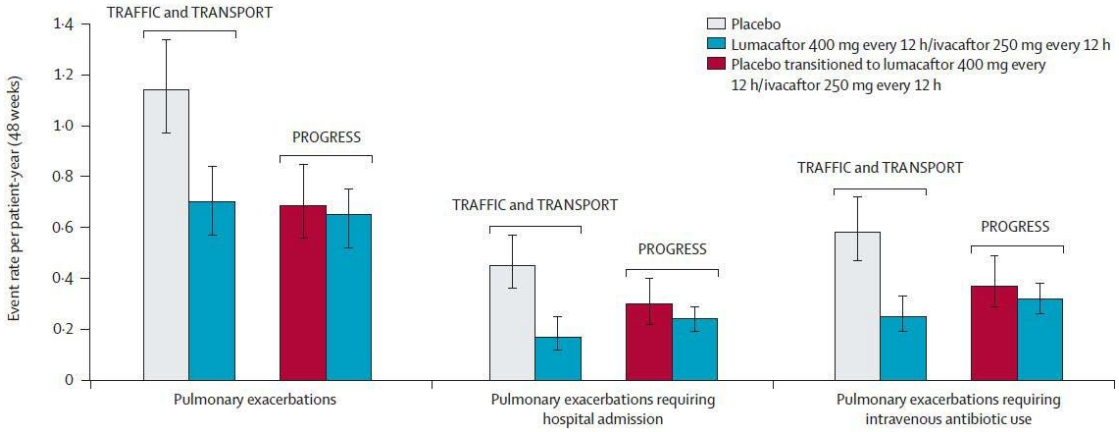
The absolute change in CFQ-R Respiratory Domain Score (points) for patients treated with ORKAMBI for 24 weeks in Study 809-103 (TRAFFIC) or Study 809-104 (TRANSPORT) remained above baseline at Week 72 (LS mean was 5.7, 95% CI 3.8 to 7.5). For patients who transitioned to ORKAMBI, a similar initial response was observed, with improvement at Week 72 (LS mean 3.3, 95% CI 0.7 to 5.9). Mean Respiratory Domain Score remained above pretreatment baseline in both groups up to Week 96 (Figure 5).

Figure 5. Absolute change in CFQ-R Respiratory Domain Score (points) at each visit



Through extension Week 96, the annualized rate (to 48 weeks) of pulmonary exacerbations remained low in patients that continued on ORKAMBI from Study 809-103 (TRAFFIC) or Study 809-104 (TRANSPORT) (0.65, 95% CI 0.56-0.75 events per patient year). For patients who transitioned from placebo to active treatment, the rate was reduced to a similar level (0.69, 95% CI 0.56-0.85). Similarly, the subsets of pulmonary exacerbations that required hospital admission remained low in patients that continued on ORKAMBI from Study 809-103 (TRAFFIC) or Study 809-104 (TRANSPORT) (0.24, 95% CI 0.19-0.29 events per patient year). For patients who transitioned from placebo to active treatment, the rate was reduced to a similar level (0.30, 95% CI 0.22- 0.40). The subsets of pulmonary exacerbations that required intravenous antibiotics remained low in patients that continued on ORKAMBI from Study 809-103 or Study 809-104 (0.32, 95% CI 0.26-0.38 events per patient year). For patients who transitioned from placebo to active treatment, the rate was reduced to a similar level (0.37, 95% CI 0.29-0.49) (Figure 6).

Figure 6. Pulmonary Exacerbations from TRAFFIC, TRANSPORT and PROGRESS



<u>Studies in patients aged 6 through 11 years</u>
The pharmacokinetic profile, safety, and efficacy of lumacaftor/ivacaftor in patients aged 6 through 11 years with CF who are homozygous for the *F508del* mutation in the *CFTR* gene are supported by a partial extrapolation from adequate and well-controlled studies of

lumacaftor/ivacaftor in patients 12 years and older [Study 809-103 (TRAFFIC) and Study 809-104 (TRANSPORT)], with additional data from two 24-week (an open-label, Phase 3 clinical study in 58 patients aged 6 through 11 years and a placebo- controlled, Phase 3 clinical study in 204 patients with CF aged 6 through 11 years).

Study 809-109: Study in patients 6 through 11 years old with CF who are homozygous for the F508del mutation in the CFTR *gene*

Study 809-109 was a 24-week, placebo-controlled, Phase 3 clinical study in 204 patients with CF aged 6 through 11 years old (mean age 8.8 years). Study 809-109 evaluated subjects with Lung Clearance Index ($LCI_{2.5}$) ≥7.5 at the initial screening visit (mean $LCI_{2.5}$ 10.28 at baseline [range: 6.55 to 16.38]) and $ppFEV_1$ ≥70 at screening (mean ppFEV1 89.8 at baseline [range: 48.6 to 119.6]). Lung Clearance Index (LCI) is a measure of lung function via exhalation and removal of a tracer gas and is calculated using multiple breath washout (MBW) technique. LCI is sensitive for early disease progression and small airway abnormalities.

Patients received either lumacaftor 200 mg/ivacaftor 250 mg every 12 hours (N=103) or placebo (N=101) in addition to their prescribed CF therapies. Patients who had 2 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 times the ULN), or ALT or AST >5 times ULN, or total bilirubin >2 times ULN were excluded.

The primary efficacy endpoint was absolute change in $LCI_{2.5}$ from baseline through Week 24. Key secondary endpoints included average absolute change from baseline in sweat chloride at Day 15 and Week 4 and at Week 24 (see Section 5.1 PHARMACODYNAMIC PROPERTIES), absolute change from baseline in BMI at Week 24, absolute change from baseline in CFQ-R Respiratory Domain through Week 24. These results are presented in Table 7 below:

Table 7: Summary of primary and key secondary outcomes in Study 809-109

		Placebo (N=101)	**LUM 200 mg/IVA 250 mg q12h (N=103)**
Primary Endpoint			
Absolute change in Lung Clearance Index ($LCI_{2.5}$) from baseline through Week 24	Treatment difference	–	-1.09 (*P*<0.0001)
	Within-group change	0.08 (*P*=0.5390)	-1.01 (*P*<0.0001)
Key Secondary Endpoints*			
Absolute change in BMI-for-age z-score at Week 24 at Week 24 (kg/m^2)	Treatment difference	–	0.03 (*P*=0.5648)
	Within-group change	0.05 (*P*=0.1739)	0.08 (*P*=0.0310)
Absolute change in CFQ-R Respiratory Domain Score through Week 24 (points)	Treatment difference	–	2.5 (*P*=0.0628)
	Within-group change	3.0 (*P*=0.0035)	5.5 (*P*<0.0001)
Absolute percent predicted FEV_1 ($ppFEV_1$) from baseline through Week 24 (percent points)	Treatment difference	–	2.4 (*P*=0.0182)
	Within-group change	1.1 (*P*=0.1483)	-1.3 (*P*=0.0899)

* Study included key secondary and other secondary endpoints

Study 809-011 (Part B): Safety and tolerability study in paediatric patients with CF aged 6 through 11 years homozygous for the F508del mutation in the CFTR *gene*

Study 809-011 evaluated subjects aged 6 through 11 years at screening, with a screening $ppFEV_1$ ≥40 and weight >15 kg. Subjects had a mean baseline $ppFEV_1$ of 91.4 (range: 55 to 122.7) and a mean baseline $LCI_{2.5}$ of 9.99.

Patients were administered lumacaftor 200 mg/ivacaftor 250 mg every 12 hours with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline). In order to evaluate off drug effects, patients had a safety follow-up visit following a 2-week washout period.

Secondary endpoints evaluated were average absolute change from baseline in sweat chloride at Day 15 and Week 4 (see Section 5.1 PHARMACODYNAMIC PROPERTIES), absolute change from baseline in weight, body mass index (BMI), height and their z-scores, Cystic Fibrosis Questionnaire-Revised (CFQ-R) at 24 weeks of treatment, and absolute change in sweat chloride from Week 24 at Week 26. Lung Clearance Index ($LCI_{2.5}$) was assessed as an exploratory endpoint. Spirometry ($ppFEV_1$) was assessed as a planned safety endpoint. These results are presented in Table 8 below.

Table 8: Effect of ORKAMBI on endpoints in Study 809-011 (Part B)

LS Mean Absolute Changes from Baseline	
Endpoint	**Week 24 (N=58)**
Secondary Endpoints	
BMI-for-age z-scores (unit)	0.15
Weight-for-age z-scores (unit)	0.13
Height-for-age z-score	0.03
CFQ-R Respiratory Domain Score (Points)	5.4
Other Endpoints	
$ppFEV_1$ (Percentage Points) at Week 24*	2.5
$ppFEV_1$ (Percentage Points) from Week 24 at Week 26†	-3.2
Exploratory Endpoint	
Lung Clearance Index ($LCI_{2.5}$)**	-0.88

* Assessed as a planned safety endpoint and also a Pharmacodynamic endpoint at Week 24 and at Week 26.
** Treatment-related decreases in LCI from baseline reflect improvements in small airway obstruction.
† After a 2-week washout period

Study 809-110: Long-term safety and efficacy rollover trial

Study 809-110 was a Phase 3, parallel-group, multicenter, rollover extension study in patients with CF that included patients aged 6 years and older from Studies 809-109 and 809-011 (Part B). This extension trial was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 262 patients who received any treatment in Studies 809-109 and 809-011 (Part B), 239 (91%) were dosed and received active treatment (lumacaftor 200 mg q12h/ivacaftor 250 mg q12h or lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) in Study 809-110 for up to an additional 96 weeks (i.e., up to a total of 120 weeks).

Patients treated with lumacaftor/ivacaftor in Studies 809-109 or 809-011 (Part B) showed that the effect on secondary efficacy endpoints was consistent with parent studies, from Studies 809-109 and 809-011 (Part B) baseline after an additional 96 weeks through Study 809-110. For patients who transitioned from placebo to active treatment, similar effects on secondary efficacy endpoints as those observed in patients treated with lumacaftor/ivacaftor in parent Study 809-109 or 809-011 (Part B) were seen.

Study 809-115: Safety and tolerability study in paediatric patients with CF aged 2 through 5 years homozygous for the F508del mutation in the CFTR *gene*

Study 809-115 evaluated 60 patients aged 2 through 5 years for 24 weeks. Patients were administered granules every 12 hours, at a dose of lumacaftor 100 mg/ivacaftor 125 mg granules for patients weighing less than 14 kg or lumacaftor 150 mg/ivacaftor 188 mg for patients weighing 14 kg or greater, in addition to their prescribed CF therapies. Secondary endpoints are included in Table 9. PK effects are described in Table 11; effects on sweat chloride are described in Section 5.1 (see PHARMACODYNAMIC PROPERTIES); safety data are described in Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Table 9: Summary of secondary outcomes in Study 809-115

Secondary endpoints*	**ORKAMBI**
Absolute change from baseline in BMI-for-age-z-score	n=57 0.29 95% CI: 0.14, 0.45
Absolute change from baseline in weight-for-age z-score	n=57 0.26 95% CI: 0.15, 0.38
Absolute change from baseline in stature-for-age z-score	n=57 0.09 95% CI: 0.02, 0.15
Absolute change from baseline in fecal elastase-1 (FE-1) levels (µg/g)**	n=35 52.6 95% CI: 22.5, 82.7
Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT) (ng/mL)***	n=55 -130.2 95% CI: -192.3, -68.1

Lung Clearance Index ($LCI_{2.5}$) n=17	n=17 -0.58 95% CI: -1.17, 0.02

[*] For all endpoints listed, absolute change from baseline is the mean absolute change from baseline at Week 24, except IRT which was through Week 24.
[**] Three of the 48 patients who had Fecal Elastase-1 values <100 µg/g at baseline achieved a level of ≥200 µg/g at Week 24.
[***] Reported value is the average change from baseline through Week 24.

Study 809-116: Long-term safety and pharmacodynamic rollover study

Study 809-116 was a Phase 3, open-label, multicenter, rollover extension study in patients with CF that included patients aged 2 years and older from Study 809-115. This study was designed to evaluate the safety and pharmacodynamics of long-term treatment of lumacaftor/ivacaftor. Of the 60 patients who received any treatment in Study 809-115, 57 were dosed and received active treatment (lumacaftor 100 mg/ivacaftor 125 mg q12h, lumacaftor 150 mg/ivacaftor 188 mg q12h, or lumacaftor 200 mg/ivacaftor 250 mg q12h depending on age and weight of the patient) in Study 809-116 for up to an additional 96 weeks (i.e., up to a total of 120 weeks).

Patients treated with lumacaftor/ivacaftor in Study 809-115 showed that the change in sweat chloride was maintained with respect to Study 809-115 baseline after an additional 96 weeks through Study 809-116. In addition, improvements in growth parameters (BMI, weight, stature and associated z-scores) were maintained through Study 809-116.

Study 809-122: Safety and pharmacokinetic study in patients aged 1 to less than 2 years with CF who are homozygous for the F508del-CFTR mutation

Trial 122 was a single-arm, uncontrolled, trial evaluating the pharmacokinetic profile, pharmacodynamic effects and safety of lumacaftor/ivacaftor in 46 patients with CF aged 1 to less than 2 years (mean age at baseline18.1 months). The pharmacodynamic effects observed in this study are similar to effects observed in patients aged 12 years and older (studies 809-103 and 809-104). The efficacy of lumacaftor/ivacaftor in patients aged 1 to less than 2 years is extrapolated from patients aged 12 years and older.

In Study 809-122 Part B the primary endpoint of safety and tolerability was evaluated across 24 weeks. Secondary endpoints evaluated were pharmacokinetics and absolute change from baseline in sweat chloride at Week 24. According to their weight at screening, patients were administered granules mixed with food every 12 hours for 24 weeks, at a dose of lumacaftor 75 mg/ivacaftor 94 mg granules (patients weighing 7 kg <9 kg) or lumacaftor 100 mg/ivacaftor 125 mg (patients weighing 9 kg to <14 kg) or lumacaftor 150 mg/ivacaftor 188 mg (patients weighing ≥14 kg), in addition to their prescribed CF therapies. In order to evaluate off-drug effects, patients had a safety follow-up visit following a 2-week washout period.

Secondary endpoints included absolute change from baseline in sweat chloride at Week 24 (see Section 5.1 PHARMACODYNAMIC PROPERTIES). Summary of additional endpoints listed in Table 10.

Table 10: Summary of additional endpoints in Study 809-122	
Additional endpoints*	**LUM/IVA**
Absolute change from baseline in BMI-for-age-z-score	n=38 0.04 95% CI: (-0.14, 0.22)
Absolute change from baseline in weight-for-age z-score	n=38 0.06 95% CI: (-0.05, 0.17)
Absolute change from baseline in weight-for-length-z-score	n=38 0.04 95% CI: (-0.13, 0.22)
Absolute change from baseline in length-for-age z-score	n=38 0.07 95% CI: (-0.11, 0.24)
Absolute change from baseline in fecal elastase-1 (FE-1) levels (mg/kg)**	n=28 73.1 95% CI: (29.4, 116.8)
Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT) (µg/L)	n=31 -295.5 95% CI: (-416.6, -174.5)

* For all endpoints listed, absolute change from baseline is the mean absolute change from baseline at Week 24.

** Of the 28 subjects with both baseline and Week 24 FE-1 levels (all of which were <200 mg/kg at baseline), 4 (14.3%) had levels ≥200 mg/kg at Week 24.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Following multiple oral doses of lumacaftor given in combination with ivacaftor, the exposure of lumacaftor generally increased proportional to dose over the range of 200 mg to 800 mg every 24 hours. The exposure of lumacaftor increased approximately 2-fold when given with fat-containing food relative to fasted conditions. The median (range) T_{max} of lumacaftor is approximately 4.0 hours (2.0; 9.0) in the fed state.

Following multiple oral dose administration of ivacaftor in combination with lumacaftor, the exposure of ivacaftor generally increased with doses from 150 mg every 12 hours to 250 mg every 12 hours. The exposure of ivacaftor when given in combination with lumacaftor increased approximately 3-fold when given with fat-containing food. Therefore, ORKAMBI should be administered with fat-containing food. The median (range) T_{max} of ivacaftor is approximately 4.0 hours (2.0; 6.0) in the fed state.

Distribution
Lumacaftor is more than 99% bound to plasma proteins, primarily to albumin. After oral administration of 400 mg every 12 hours in patients with CF in a fed state, the typical apparent volumes of distribution for the central and peripheral compartments (CV) were estimated to be 23.5 L (48.7%) and 33.3 L (30.5%), respectively.

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. After oral administration of ivacaftor 250 mg every 12 hours in combination with lumacaftor, the typical apparent volumes of distribution for the central and peripheral compartments (CV) were estimated to be 95.0 L (53.9%) and 201 L (26.6%), respectively.

Metabolism
Lumacaftor is not extensively metabolised in humans with the majority of lumacaftor excreted unchanged in the faeces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolised via oxidation and glucuronidation, with CYP3A4 and CYP2C8 involved. The main metabolite formed, M28, is not pharmacologically active.

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 of ivacaftor 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 of lumacaftor, the majority of lumacaftor (51%) is excreted unchanged in the faeces. There was negligible urinary excretion of lumacaftor as unchanged drug. The apparent terminal half-life is approximately 26 hours. The typical apparent clearance, CL/F (CV), of lumacaftor was estimated to be 2.38 L/hr (29.4%) for patients with CF.

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the faeces after metabolic conversion. There was negligible urinary excretion of ivacaftor as unchanged drug. In healthy subjects, the half-life of ivacaftor when given with lumacaftor is approximately 9 hours. The typical CL/F (CV) of ivacaftor when given in combination with lumacaftor was estimated to be 25.1 L/hr (40.5%) for patients with CF.

Special populations
The exposures are similar between adults and the paediatric population based on population pharmacokinetics (PK) analyses. Data for patients aged 1 to less than 18 years are presented in Table 11 below:

Table 11: Mean (SD) lumacaftor and ivacaftor exposure by age group

Age Group	Weight	Dose	Mean lumacaftor (SD) AUC_{ss} (µg·h/mL)	Mean ivacaftor (SD) AUC_{ss} (µg·h/mL)
Patients aged 1 to less than 2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg sachet every 12 hours	234[a]	7.98[a]
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours	191 (40.6)	5.35 (1.61)
	≥14 kg	lumacaftor 150 mg/ivacaftor	116[a]	5.82[a]

		188 mg sachet every 12 hours		
Patients aged 2 through 5 years	<14 kg	lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours	180 (45.5)	5.92 (4.61)
Patients aged 2 through 5 years	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg sachet every 12 hours	217 (48.6)	5.90 (1.93)
Patients aged 6 through 11 years	-	lumacaftor 200 mg/ivacaftor 250 mg every 12 hours	203 (57.4)	5.26 (3.08)
Patients aged 12 to <18 years	-	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	253 (68.6)	3.84 (1.54)

[a] Values based on data from a single patient; standard deviation not reported.

Hepatic impairment

Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had higher exposures ($AUC_{0\text{-}12hr}$ by approximately 50% and C_{max} by approximately 30%) compared with healthy subjects matched for demographics. The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on pharmacokinetics of lumacaftor given in combination with ivacaftor has not been studied, but the increase in exposure is expected to be less than 50% (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Renal impairment

Pharmacokinetic studies have not been performed with ORKAMBI in patients with renal impairment. In a human pharmacokinetic study with lumacaftor alone, there was minimal elimination of lumacaftor and its metabolites in urine (only 8.6% of total radioactivity was recovered in the urine with 0.18% as unchanged parent). In a human pharmacokinetic study with ivacaftor alone, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Gender
The effect of gender was evaluated using a population pharmacokinetics analysis of data from clinical studies of lumacaftor given in combination with ivacaftor. Results indicate no clinically relevant difference in pharmacokinetic parameters for lumacaftor and ivacaftor between males and females. No dose adjustments of ORKAMBI are necessary based on gender.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Both lumacaftor and ivacaftor were 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
A two-year study in Sprague-Dawley rats and a 26-week study in transgenic Tg.rasH2 mice were conducted to assess the carcinogenic potential of lumacaftor. No evidence of tumourigenicity by lumacaftor was observed in rats at oral doses up to 1000 mg/kg/day (yielding approximately 5 and 13 times the plasma AUC for lumacaftor in patients at the MRHD in males and females, respectively). No evidence of tumourigenicity was observed in Tg.rasH2 mice at lumacaftor oral doses up to 1500 and 2000 mg/kg/day in female and male mice, respectively. Plasma exposures to lumacaftor in mice at these doses were approximately 5- and 3.5-fold higher than the plasma levels of lumacaftor measured in humans following lumacaftor/ivacaftor therapy.

Two-year studies in mice and rats to assess carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dose (200 mg/kg/day, the highest dose tested) were approximately 10- to 18-fold higher than the plasma levels measured in 6-11 years old children following ORKAMBI therapy, and at least 1.1- to 2.2 -fold higher with respect to the summed AUCs for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in rats at the non-carcinogenic dose (50 mg/kg/day, the highest dose tested) were approximately 41- to 74-fold higher than the plasma levels measured in humans following ORKAMBI therapy, and 6 - to 8 -fold higher with respect to the summed AUCs for ivacaftor and its major metabolites. As ORKAMBI therapy in ≥12 years old patients is associated with lower exposure to ivacaftor and its major metabolites than in 6–11 years old, higher exposure margins (increased by a factor of 1.6) apply to older children and adults.

Juvenile rats toxicity
Cataracts were seen in juvenile rats treated with ivacaftor from postnatal Day 7 through 35 at oral dose levels of 10 mg/kg/day and higher, yielding exposure to ivacaftor and its major metabolites approximately 4–6.5 times lower than in 6–11 years old patients and 2.5–4 times lower than in older patients at the maximum recommended human dose with ORKAMBI (based on summed AUCs). This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ORKAMBI tablets contain the following inactive ingredients: microcrystalline cellulose; croscarmellose sodium; hypromellose acetate succinate; povidone; sodium lauryl sulfate; magnesium stearate; Opadry II Pink 85F140026 (PI# 110227); Opacode monogramming ink S-1-17823 BLACK (PI# 12108).

ORKAMBI granules contain the following inactive ingredients: microcrystalline cellulose; hypromellose acetate succinate; croscarmellose sodium; sodium lauryl sulfate; povidone.

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
ORKAMBI 100/125 tablets and ORKAMBI 200/125 tablets are packaged in a thermoform [polychlorotrifluoroethylene (PCTFE)] blister with a paper-backed foil lidding. There are four tablets in each blister strip. Seven strips are included in each weekly carton (28 tablets). Four cartons are contained in each ORKAMBI 100/125 or 200/125 box, totalling 112 tablets.

Granules
ORKAMBI 75/94, ORKAMBI 100/125 and ORKAMBI 150/188 granules in sachet are packaged in a foil laminate [biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE)] sachet. There are 14 sachets in a wallet, and 4 wallets in a carton, totalling 56 sachets.

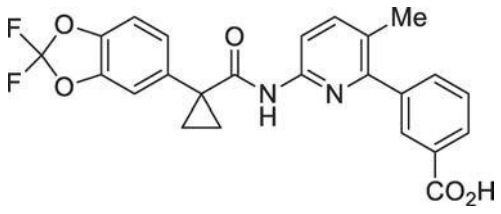
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

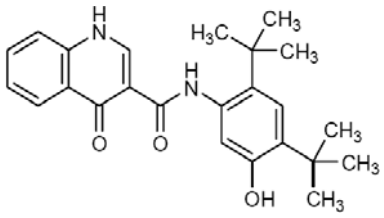
6.7 PHYSICOCHEMICAL PROPERTIES

The active ingredients in ORKAMBI tablets are lumacaftor, which has the following chemical name: 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5yl) cyclopropyl]carbonyl}amino) - 3-methylpyridin-2-yl]benzoic acid, and ivacaftor, which has the following chemical name: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide.

Chemical structure
The structural formulas are:



lumacaftor



ivacaftor

The empirical formula for lumacaftor is $C_{24}H_{18}F_2N_2O_5$ and for ivacaftor is $C_{24}H_{28}N_2O_3$.

The molecular weights for lumacaftor and ivacaftor are 452.41 and 392.49, respectively.

The pKa values of lumacaftor are 2.51 and 4.28. The log D value of lumacaftor is 2.29 at pH=7.4 and 25°C. 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.

Lumacaftor is a white to off-white powder that is practically insoluble in water (0.02 mg/mL). Ivacaftor is a white to off-white powder that is practically insoluble in water (<0.05 µg/mL).

CAS number
Lumacaftor: 936727-05-8
Ivacaftor: 873054-44-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Vertex Pharmaceuticals (Australia) Pty Ltd
Suite 3, Level 3
601 Pacific Highway
St Leonards NSW 2065 Australia
Telephone: 1800 179 987

9 DATE OF FIRST APPROVAL

08 March 2016

10 DATE OF REVISION

3 March 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8 Adverse effects (Undesirable effects)	Inclusion of summary of safety data based on outcomes of Study 809-124.