

NEW ZEALAND DATA SHEET
ORKAMBI® (LUMACAFITOR AND IVACAFITOR)
TABLETS AND GRANULES

1 ORKAMBI film-coated tablets and granules

ORKAMBI (lumacaftor 200 mg and ivacaftor 125 mg) film-coated tablets
ORKAMBI (lumacaftor 100 mg and ivacaftor 125 mg) film-coated tablets
ORKAMBI (lumacaftor 150 mg and ivacaftor 188 mg) granules
ORKAMBI (lumacaftor 100 mg and ivacaftor 125 mg) granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

Each film-coated tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor as a fixed dose combination.

Or

Each film-coated tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor as a fixed dose combination.

Granules

Each granule sachet contains 150 mg lumacaftor and 188 mg ivacaftor.

Or

Each granule sachet contains 100 mg lumacaftor and 125 mg ivacaftor.

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

3 PHARMACEUTICAL FORM

ORKAMBI 200 mg/125 mg (lumacaftor/ivacaftor) film-coated tablets are supplied as pink, oval-shaped tablets (14 x 8.4 x 6.8 mm). Each tablet is printed with “2V125” in black ink on one side and plain on the other.

ORKAMBI 100 mg/125 mg (lumacaftor/ivacaftor) film-coated tablets are supplied as pink, oval-shaped tablets (14 x 7.6 x 4.9 mm). Each tablet is printed with “1V125” in black ink on one side and plain on the other.

ORKAMBI 150 mg/188 mg and ORKAMBI 100 mg /125 mg (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 2 years 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.

For standard dosing recommendations see Table 1.

Table 1: Recommended dose of ORKAMBI in patients aged 2 years and older		
Age	ORKAMBI dose	Total daily dose
2 through 5 years and weighing less than 14 kg	One lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours	lumacaftor 200 mg/ivacaftor 250 mg
2 through 5 years and weighing 14 kg and greater	One lumacaftor 150 mg/ivacaftor 188 mg sachet every 12 hours	lumacaftor 300 mg/ivacaftor 376 mg
6 through 11 years	Two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours	lumacaftor 400 mg/ivacaftor 500 mg
12 years and older	Two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours	lumacaftor 800 mg/ivacaftor 500 mg

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, 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 include pureed fruits, flavored yogurt or pudding, and milk 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 UNDESIRABLE EFFECTS).

Hepatic impairment	Dose adjustment	Total daily dose
Mild hepatic impairment (Child-Pugh Class A)	No dose adjustment	<i>For patients aged 2 through 5 years and <14 kg</i> lumacaftor 200 mg + ivacaftor 250 mg
		<i>For patients aged 2 through 5 years and ≥14 kg</i> lumacaftor 300 mg + ivacaftor 376 mg
		<i>For patients aged 6 through 11 years</i> 400 mg lumacaftor + 500 mg ivacaftor
		<i>For patients aged 12 years and older</i> 800 mg lumacaftor + 500 mg ivacaftor
Moderate hepatic impairment (Child-Pugh Class B)	1 sachet per day	<i>For patients aged 2 through 5 years and <14 kg</i> lumacaftor 100 mg + ivacaftor 125 mg <i>For patients aged 2 through 5 years and ≥14 kg</i> lumacaftor 150 mg + ivacaftor 188 mg
	2 tablets in the morning + 1 tablet in the evening (12 hours later)	<i>For patients aged 6 through 11 years</i> 300 mg lumacaftor + 375 mg ivacaftor <i>For patients aged 12 years and older</i> 600 mg lumacaftor + 375 mg ivacaftor
Severe hepatic impairment (Child-Pugh Class C)	1 sachet per day or less frequently	<i>For patients aged 2 through 5 years and <14 kg</i> lumacaftor 100 mg + ivacaftor 125 mg <i>For patients aged 2 through 5 years and ≥14 kg</i> lumacaftor 150 mg + ivacaftor 188 mg
	1 tablet every 12 hours or less frequently	<i>For patients aged 6 through 11 years</i> 200 mg lumacaftor + 250 mg ivacaftor (or a lower dose) <i>For patients aged 12 years and older</i> 400 mg lumacaftor + 250 mg ivacaftor (or a lower dose)

Use in patients with advanced lung dysfunction

Clinical experience in patients with ppFEV₁ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. In Trial 5, patients aged 12 years and older with advanced lung disease (ppFEV₁ <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 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 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 UNDESIRABLE EFFECTS).

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 UNDESIRABLE EFFECTS, and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 FEV₁ (ppFEV₁) <40. Clinical experience in patients with ppFEV₁ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy (See Section, 4.8 UNDESIRABLE EFFECTS, and Section 5.1 PHARMACODYNAMIC PROPERTIES: CLINICAL EFFICACY AND SAFETY). 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 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.

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.

Mood disturbances

Effects on mood and behaviour such as anxiety, low mood, sleep disturbance, and forgetfulness have occasionally been reported in people with cystic fibrosis treated with Orkambi.

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

A causal relationship has not been established with Orkambi treatment, and some patients have been reported to recover with continued treatment. Patients and caregivers should be alerted to the need to monitor for new or worsening symptoms and seek medical advice if they occur.

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

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 the Elderly

Clinical studies of ORKAMBI did not include patients age 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 Section 5.1 PHARMACODYNAMIC PROPERTIES: CLINICAL EFFICACY AND SAFETY). 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 ↓ montelukast Due to the induction of CYP3A/2C8/2C9 by LUM	No dose adjustment for montelukast is recommended. Appropriate clinical monitoring should be employed, as is reasonable, when co-administered with lumacaftor/ivacaftor. Lumacaftor/ivacaftor may decrease the exposure of montelukast, which may reduce its efficacy.
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 ↓ clarithromycin, telithromycin Due to induction of CYP3A by LUM	No dose adjustment of lumacaftor/ivacaftor is recommended when clarithromycin or telithromycin are initiated in patients currently taking lumacaftor/ivacaftor. 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.

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
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.
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-inflammatory: 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 ↔ rifampicin, rifapentine	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.

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: cyclosporin, everolimus, sirolimus, tacrolimus (used after organ transplant)	↔ LUM, IVA ↓ cyclosporin, 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 (<i>Hypericum perforatum</i>)	↔ 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

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.

Breast-feeding

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.

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).

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 UNDESIRABLE EFFECTS

Summary of the safety profile

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 2 double-blind, placebo-controlled, Phase 3 clinical studies, each with 24 weeks of treatment (Trial 1 TRAFFIC and Trial 2 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 <i>F508del</i> Mutation in the <i>CFTR</i> Gene		
	LUM/IVA Total	Placebo
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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 lumacaftor/ivacaftor-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 disorders	very common	Nasal congestion, Dyspnoea, Productive cough, Sputum increased
	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 (Trial 4) in 1029 patients age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene, were consistent with in Trials 1 and 2. The respiratory events in treatment naïve patients who were initiated on LUM/IVA in Trial 4 were comparable to those who were initiated on LUM/IVA in preceding Trials 1 and 2.

Studies in patients aged 6 through 11 years

The safety profile observed in studies in patients 6-11 years old (Trial 6 and 7) was similar to that observed in Trials 1 and 2.

Adverse reactions that are not listed in Table 5, and that occurred in $\geq 5\%$ of lumacaftor/ivacaftor- treated patients with an incidence of $\geq 3\%$ higher than placebo (Trial 7) 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%).

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 (Trial 8) the safety profile was generally consistent to that observed in studies in patients aged 6-11 years.

Description of Selected Adverse Reactions

Hepatobiliary Events

Patients over 12 years of age

During the 24-week, placebo-controlled, Phase 3 studies, 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 7 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 (Trial 7), 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 permanently.

During the 24 week, placebo-controlled Phase 3 clinical study in 204 patients aged 6 through 11 years (Trial 6), 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 permanently due to transaminase elevations.

During the 24-week, open-label Phase 3 clinical study in 60 patients aged 2 through 5 years (Trial 8), 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 permanently due to transaminase elevations.

Respiratory Events

Patients over 12 years of age

During the 24-week, placebo-controlled, Phase 3 studies, 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 FEV₁. 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 (Trial 5) in 46 patients aged 12 years and older with advanced lung disease (ppFEV₁ <40) [mean ppFEV₁ 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 (Trial 7) in 58 patients aged 6 through 11 years (mean baseline ppFEV₁ was 91.4), the incidence of respiratory adverse reactions was 6.9% (4/58).

During the 24 week, placebo-controlled Phase 3 clinical study (Trial 6) in patients aged 6 through 11 years (mean baseline ppFEV₁ 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 ppFEV₁ 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, 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

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 ppFEV₁. Some of these events were serious and led to lumacaftor/ivacaftor treatment discontinuation (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine 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 <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Respiratory system, Other respiratory system products; ATC code: R07AX30.

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.

Pharmacodynamic effects

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 (Trial 7 VX13-809-011) and as part of a 24-week, placebo- controlled Phase 3 clinical study (Trial 6 VX14-809-109) 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 Trial 7, 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 Trial 6, treatment with lumacaftor 200 mg/ivacaftor 250 mg q12h for 24 weeks demonstrated a statistically significant 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; $P < 0.0001$). The treatment difference (LS mean) in sweat chloride for the absolute change at Week 24 as compared to placebo was -24.9 mmol/L ($P < 0.0001$).

Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24-week, open label Phase 3 clinical study (Trial 8) 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.

Clinical efficacy and safety

Trials 1 and 2 in Patients With CF Who are Homozygous for the F508del Mutation in the CFTR Gene

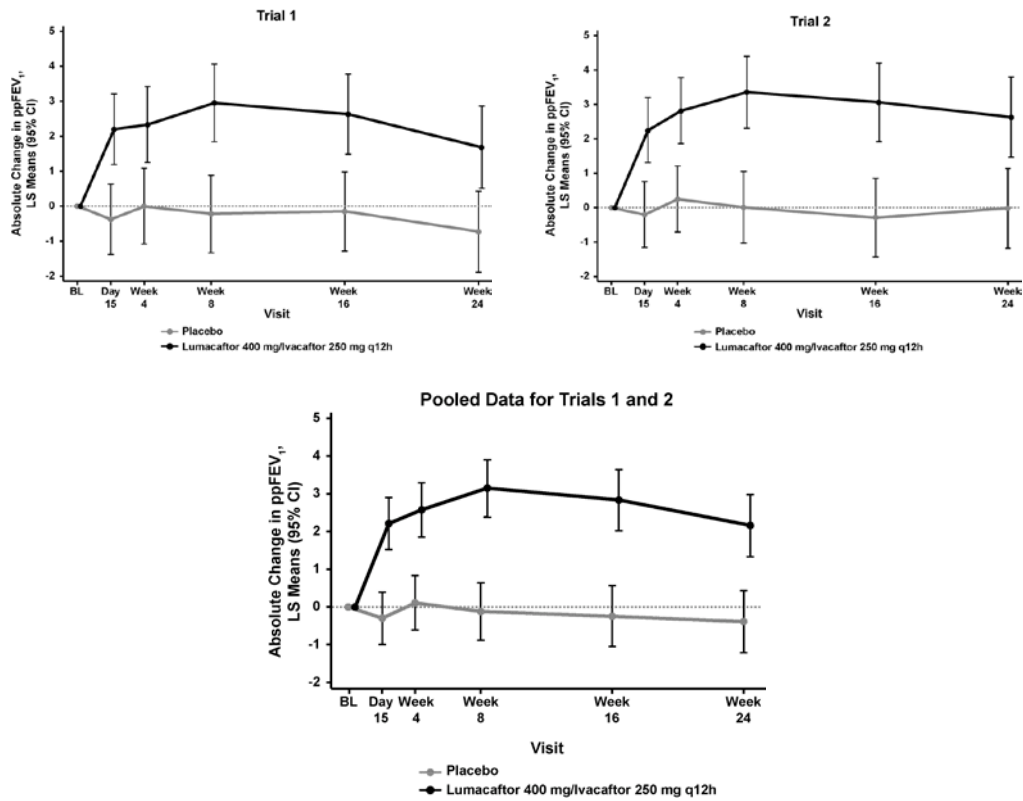
The efficacy of ORKAMBI in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomised, double-blind, placebo-controlled clinical trials of 1108 clinically stable patients with CF, in which 737 patients were randomised to and dosed with lumacaftor/ivacaftor. 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.

Trial 1, VX12-809-103 (TRAFFIC) evaluated 549 patients with CF who were aged 12 years and older (mean age 25.1 years) with percent predicted FEV₁ (ppFEV₁) at screening between 40-90 [mean ppFEV₁ 60.7 at baseline (range: 31.1 to 94.0)]. **Trial 2, VX 12-809-104 (TRANSPORT)** evaluated 559 patients aged 12 years and older (mean age 25.0 years) with ppFEV₁ at screening between 40-90 [mean ppFEV₁ 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 ppFEV₁ 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 ppFEV₁ 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 $\geq 5\%$ relative change from baseline in ppFEV₁ 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 ppFEV₁ (Table 6). The treatment difference between lumacaftor/ivacaftor 400 mg/250 mg q12h and placebo for the mean absolute change (95% CI) in ppFEV₁ 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 Trial 1 ($P=0.0003$) and 3.0 percentage points (1.6, 4.4) in Trial 2 ($P<0.0001$). Mean improvement in ppFEV₁ was rapid in onset (Day 15) and sustained throughout the 24-week treatment period (Figure 1). Improvements in ppFEV₁ were observed regardless of age, disease severity, sex, and geographic region. The Phase 3 trials of lumacaftor/ivacaftor included 81 patients with ppFEV₁ <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 ppFEV₁ ≥ 40 . See Table 6 for a summary of primary and key secondary outcomes in Trials 1 and 2.

Figure 1. Absolute Change From Baseline at Each Visit in Percent Predicted FEV₁ in Trial 1, Trial 2, and Pooled Data for Trials 1 and 2.



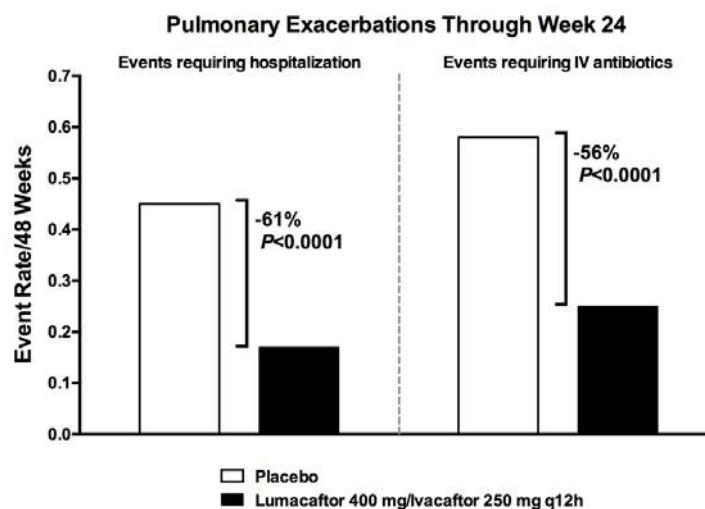
LS, least squares; q12h, every 12 hours.

		Trial 1		Trial 2		Pooled (Trial 1 and Trial 2)	
		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 ppFEV₁ at Week 24[†] (percentage points)	Treatment difference	–	2.6 (<i>P</i> =0.0003) [‡]	–	3.0 (<i>P</i> <0.0001) [‡]	–	2.8 (<i>P</i> <0.0001)
	Within-group change	-0.44 (<i>P</i> =0.4002)	2.2 (<i>P</i> <0.0001)	-0.15 (<i>P</i> =0.7744)	2.9 (<i>P</i> <0.0001)	-0.32 (<i>P</i> <0.3983)	2.5 (<i>P</i> <0.0001)
Relative change in ppFEV₁ at Week 24[†] (%)	Treatment difference	–	4.3 (<i>P</i> =0.0006) [‡]	–	5.3 (<i>P</i> <0.0001) [‡]	–	4.8 (<i>P</i> <0.0001)
	Within-group change	-0.34 (<i>P</i> =0.7113)	4.0 (<i>P</i> <0.0001)	0 (<i>P</i> =0.9983)	5.3 (<i>P</i> <0.0001)	-0.17 (<i>P</i> =0.8030)	4.6 (<i>P</i> <0.0001)
Absolute change in BMI at Week 24 (kg/m²)	Treatment difference	–	0.13 (<i>P</i> =0.1938)	–	0.36 (<i>P</i> <0.0001) [‡]	–	0.24 (<i>P</i> =0.0004)
	Within-group change	0.19 (<i>P</i> =0.0065)	0.32 (<i>P</i> <0.0001)	0.07 (<i>P</i> =0.2892)	0.43 (<i>P</i> <0.0001)	0.13 (<i>P</i> =0.0066)	0.37 (<i>P</i> <0.0001)
Absolute change in CFQ-R Respiratory Domain Score at Week 24 (points)	Treatment difference	–	1.5 (<i>P</i> =0.3569)	–	2.9 (<i>P</i> =0.0736)	–	2.2 (<i>P</i> =0.0512)
	Within-group change	1.1 (<i>P</i> =0.3423)	2.6 (<i>P</i> =0.0295)	2.8 (<i>P</i> =0.0152)	5.7 (<i>P</i> <0.0001)	1.9 (<i>P</i> =0.0213)	4.1 (<i>P</i> <0.0001)
Proportion of patients with ≥5% relative change in ppFEV₁ using the average of Week 16 and Week 24	%	22%	37%	23%	41%	22%	39%
	Odds ratio	–	2.06 (<i>P</i> =0.0023)	–	2.38 (<i>P</i> =0.0001)	–	2.22 (<i>P</i> <0.0001)
Number of pulmonary exacerbations through Week 24	# of events (rate per 48 wks)	112 (1.07)	73 (0.71)	139 (1.18)	79 (0.67)	251 (1.14)	152 (0.70)
	Rate ratio	–	0.66 (<i>P</i> =0.0169)	–	0.57 (<i>P</i> =0.0002)	–	0.61 (<i>P</i> <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*≤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



Trial 3: Patients With CF Who are Heterozygous for the F508del Mutation in the CFTR Gene

Trial 3 (VX09-809-102) was a multicenter, double-blind, randomised, placebo-controlled, Phase 2 trial in 125 patients with CF aged 18 years and older who had a ppFEV₁ 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 ppFEV₁ 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.

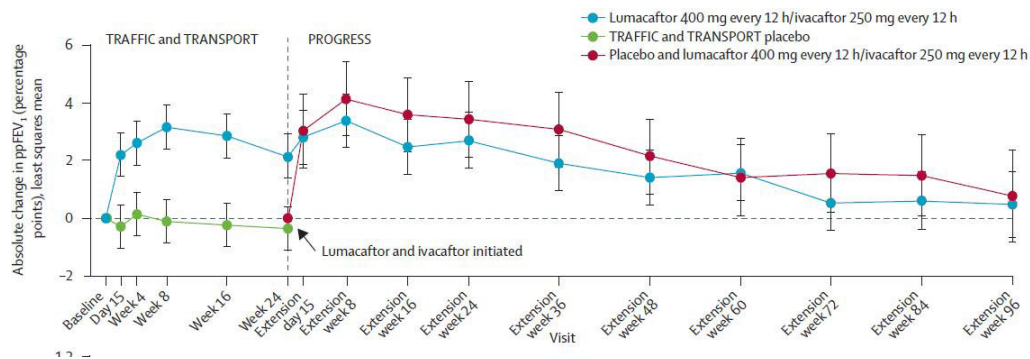
The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline at Day 56 in ppFEV₁. Treatment with ORKAMBI resulted in no significant improvement in ppFEV₁ relative to placebo in patients with CF heterozygous for the *F508del* mutation in the *CFTR* gene [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 ppFEV₁, BMI, and weight; however, there was a nominally statistically significant change in the CF respiratory symptom score.

Trial 4: Long-term Safety and Efficacy Rollover Trial

Trial 4 (VX12-809-105, 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 Trial 1 (TRAFFIC) and Trial 2 (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 Trial 1 or Trial 2, 1029 patients (93%) were dosed and received active treatment in Trial 4 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.

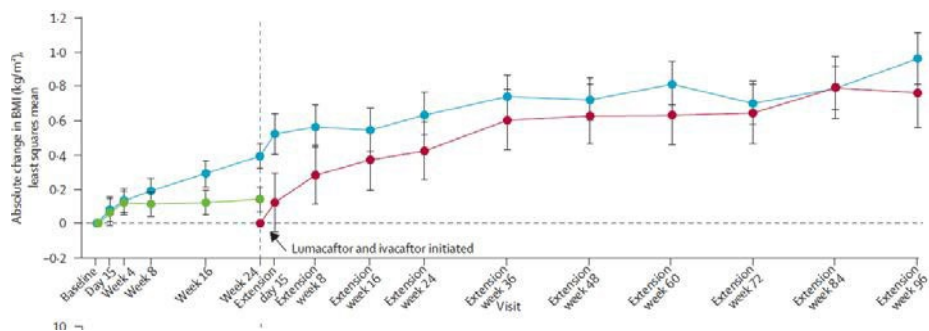
The absolute change in ppFEV₁ observed in patients treated with ORKAMBI in Trial 1 or Trial 2 remained above baseline at week 72 (LS mean 0.5, 95% CI -0.4 to 1.5). In patients who transitioned from placebo to ORKAMBI, an improvement in ppFEV₁ was observed on initiation of active treatment which was maintained 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 ppFEV₁ 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 FEV₁ at each visit



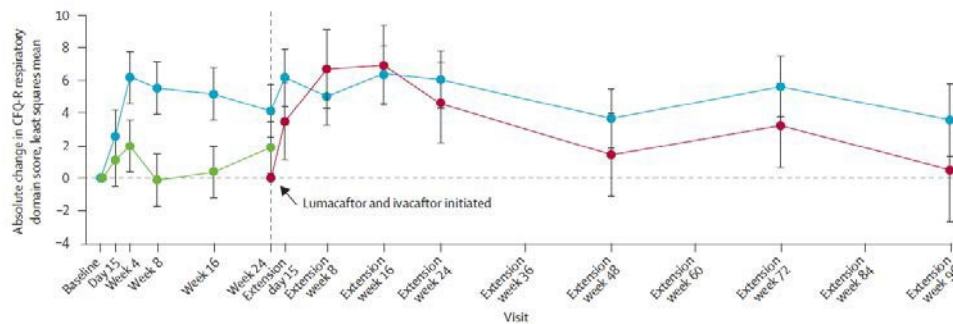
Patients treated with ORKAMBI for 24 weeks in Trial 1 or Trial 2 continued to show improvement in BMI through Trial 4. At baseline the BMI (SD) was 21.5 kg/m² (3.0). At week 72, the LS mean of absolute change from baseline was 0.69 (95% CI 0.56-0.81) in patients who remained on ORKAMBI and in patients 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/m²) at each visit



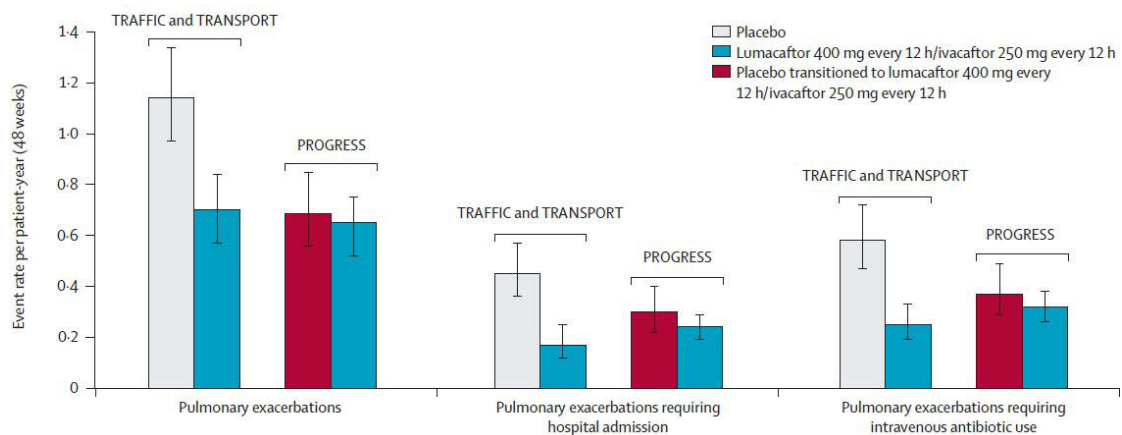
The absolute change in CFQ-R respiratory domain score (points) for patients treated with ORKAMBI for 24 weeks in Trial 1 or Trial 2 remained above baseline at week 72 (LS mean was 5.7, 95% CI 3.8 to 7.5). For patients who transitioned to ORKAMBI, a similar initial response was observed, with improvement 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 Trial 1 or Trial 2 (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 Trial 1 or Trial 2 (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 Trial 1 or Trial 2 (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



Studies in patients aged 6 through 11 years

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 (Trial 1 and Trial 2), 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).

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

Trial 6 (VX14-809-109) 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). Trial 6 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 ppFEV₁ ≥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 Trial 6			
		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/m²)	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 FEV₁ (ppFEV₁) 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			

Trial 7: Safety and tolerability study in paediatric patients with CF aged 6 through 11 years homozygous for the F508del mutation in the CFTR gene

Trial 7 (VX13-809-011) evaluated subjects aged 6 through 11 years at screening, with a screening ppFEV₁ ≥40 and weight >15 kg. Subjects had a mean baseline ppFEV₁ 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: PHARMACODYNAMIC EFFECTS), 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 (ppFEV₁) was assessed as a planned safety endpoint. These results are presented in Table 8 below.

Table 8: Effect of lumacaftor/ivacaftor on endpoints in Trial 7	
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	

Trial 8: Safety and tolerability study in paediatric patients with CF aged 2 through 5 years homozygous for the F508del mutation in the CFTR gene

Trial 8 (VX15-809-115) 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 10; effects on sweat chloride are described in Section 5.1 (see Section 5.1 PHARMACODYNAMIC PROPERTIES); safety data are described in Section 4.8 UNDESIRABLE EFFECTS.

Table 9: Summary of secondary outcomes in Trial 8	
Secondary endpoints*	LUM/IVA
Absolute change from baseline in BMI-for-age-z-score	0.29 95% CI: 0.14, 0.45
Absolute change from baseline in weight-for-age z-score	0.26 95% CI: 0.15, 0.38
Absolute change from baseline in stature-for-age z-score	0.09 95% CI: 0.02, 0.15
Absolute change from baseline in fecal elastase-1 (FE-1) levels ($\mu\text{g/g}$)**	52.6 95% CI: 22.5, 82.7
Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT) (ng/mL)***	-130.2 95% CI: -192.3, -68.1
Lung Clearance Index ($\text{LCI}_{2.5}$) 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. ** Three of the 48 patients who had Fecal Elastase-1 values $<100 \mu\text{g/g}$ at baseline achieved a level of $\geq 200 \mu\text{g/g}$ at Week 24. *** Reported value is the average change from baseline through 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 99.9% 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.

Elimination

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 2 to less than 18 years are presented in Table 10 below:

Age Group	Dose	Mean lumacaftor (SD) AUC _{ss} (µg/mL*h)	Mean ivacaftor (SD) AUC _{ss} (µg/mL*h)
Patients aged 2 through 5 years and weighing less than 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 and weighing 14 kg or greater	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 less than 18 years	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	253 (68.6)	3.84 (1.54)

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_{0-12hr} by approximately 50% and C_{max} by approximately 30%) compared with healthy subjects matched for demographics. Therefore, ORKAMBI should be reduced to 2 tablets in the morning and 1 tablet in the evening for patients with moderate hepatic impairment (Child-Pugh Class B). 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%. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening, or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment (See Section 4.4 SPECIAL WARNINGS and PRECAUTIONS FOR USE, Section 4.8 (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). Therefore, no dose adjustments for ORKAMBI are recommended for mild and moderate renal impairment. However, caution is recommended when administering ORKAMBI to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease.

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 tumorigenicity 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 tumorigenicity 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 year 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 year old patients is associated with lower exposure to ivacaftor and its major metabolites than in 6–11 year olds, 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 year 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; Opacode monogramming ink S-1-17823 BLACK.

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

ORKAMBI (200 mg lumacaftor and 125 mg ivacaftor) film-coated tablets and ORKAMBI (100 mg lumacaftor and 125 mg ivacaftor) film-coated tablets

30 months

ORKAMBI (150 mg lumacaftor and 188 mg ivacaftor) granules and ORKAMBI (100 mg lumacaftor and 125 mg ivacaftor) granules

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ORKAMBI 100/125 mg or ORKAMBI 200/125 mg film coated tablets

Packaged in a thermoform [polychlorotrifluoroethylene (PCTFE)] blister with a paper-backed foil lidding.

Pack size: There are four tablets in each blister strip. Seven strips are included in each weekly carton (28 tablets). Four cartons are contained in each box, totaling 112 tablets.

ORKAMBI 100/125 mg or ORKAMBI 150/188 mg granules in sachet

Packaged in a foil laminate [biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/ PE/Foil/PE)] sachet.

Pack size: There are 14 sachets in a wallet, and 4 wallets in a carton, totaling 56 sachets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics

P O Box 62027

Sylvia Park

AUCKLAND 1644

New Zealand

Telephone: (09) 918 5100

9 DATE OF FIRST APPROVAL

02 March 2023

10 DATE OF REVISION

04 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4 Special Warnings and Precautions for Use	Updated to include 'Mood disturbances' section