▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

For further information on the scheme, see the Information for sponsors on the TGA website.

AUSTRALIAN PRODUCT INFORMATION – TRIKAFTA® (ELEXACAFTOR/TEZACAFTOR/IVACAFTOR, IVACAFTOR) FILM–COATED TABLETS AND GRANULES

1 NAME OF THE MEDICINE

Elexacaftor, tezacaftor and ivacaftor in combination, and ivacaftor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

TRIKAFTA 100/50/75 film-coated tablets

One morning dose film-coated tablet contains elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg.
One evening dose film-coated tablet contains ivacaftor 150 mg.

Excipients with known effect: contains sugars as lactose (150 mg ivacaftor tablet).
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

TRIKAFTA 50/25/37.5 film-coated tablets

One morning dose film-coated tablet contains elexacaftor 50 mg, tezacaftor 25 mg and ivacaftor 37.5 mg.
One evening dose film-coated tablet contains ivacaftor 75 mg.

Excipients with known effect: contains sugars as lactose (75 mg ivacaftor tablet).
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

Granules

TRIKAFTA 100/50/75 granules

One morning dose sachet contains elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg.
One evening dose sachet contains ivacaftor 75 mg.

Excipients with known effect: contains sugars as lactose, contains sucralose.
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

TRIKAFTA 80/40/60 granules

One morning dose sachet contains elexacaftor 80 mg, tezacaftor 40 mg and ivacaftor 60 mg.
One evening dose sachet contains ivacaftor 59.5 mg.

Excipients with known effect: contains sugars as lactose, contains sucralose.
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Composite pack

TRIKAFTA 100/50/75 film-coated tablets
elexacaftor/tezacaftor/ivacaftor 100 mg/50 mg/75 mg tablet
Orange, capsule-shaped tablet with "T100" debossed on one side and plain on the other (7.9 mm x 15.5 mm).

ivacaftor 150 mg tablet
Light blue, capsule-shaped tablet printed with "V 150" in black ink on one side and plain on the other (16.5 mm x 8.4 mm).

TRIKAFTA 50/25/37.5 film-coated tablets
elexacaftor/tezacaftor/ivacaftor 50 mg/25 mg/37.5 mg tablet
Light orange, capsule-shaped tablet with "T50" debossed on one side and plain on the other (6.4 mm x 12.2 mm).

ivacaftor 75 mg tablet
Light blue, capsule-shaped tablet printed with "V 75" in black ink on one side and plain on the other (12.7 mm x 6.8 mm).

TRIKAFTA 100/50/75 granules and 80/40/60 granules
elexacaftor/tezacaftor/ivacaftor 100mg/50mg/75mg and 80mg/40mg/60mg granules
White to off-white, sweetened, unflavored granules approximately 2 mm in diameter.

ivacaftor 75 mg granules and 59.5 mg granules
White to off-white, sweetened, unflavored granules approximately 2 mm in diameter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRIKAFTA is indicated for the treatment of those who meet the diagnostic criteria of cystic fibrosis (CF) in patients aged 2 years and older who have at least one mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene that is responsive based on clinical or *in vitro* evidence (see section 5.1 PHARMACODYNAMIC PROPERTIES).

4.2 DOSE AND METHOD OF ADMINISTRATION

TRIKAFTA should only be prescribed by physicians with experience in the treatment of CF.

Dosage
Adults and paediatric patients aged 2 years and older should be dosed according to Table 1.

Table 1: Dosing Recommendation for Patients Aged 2 Years and Older			
Age	**Weight**	**Morning Dose**	**Evening Dose**
2 to < 6 years	< 14 kg	One sachet of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules	One sachet of ivacaftor 59.5 mg granules
2 to < 6 years	≥ 14 kg	One sachet of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules	One sachet of ivacaftor 75 mg granules
6 to <12 years	<30 kg	Two elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg tablets	One ivacaftor 75 mg tablet
6 to <12 years	≥30 kg	Two elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablets	One ivacaftor 150 mg tablet
≥12 years	-	Two elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablets	One ivacaftor 150 mg tablet

The morning and evening dose should be taken with fat-containing food, approximately 12 hours apart.

Missed dose
If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule.
If more than 6 hours have passed since:

- the missed morning dose, the patient should take the missed dose as soon as possible and should not take the evening dose. The next scheduled morning dose should be taken at the usual time.
- the missed evening dose, the patient should not take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

Method of administration
A fat-containing meal or snack should be consumed just before or just after dosing of TRIKAFTA. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. A serving size of foods appropriate for age from a recommended CF diet should be given. 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, avocado, hummus, oily fish, and soy-based products (tofu) (see section 5.2 PHARMACOKINETIC PROPERTIES).

Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Tablets
For oral use. Patients should be instructed to swallow the tablets whole.

Granules
For oral use. The entire contents of each sachet of granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. Food or liquid should be at room temperature or below. Each sachet is for single use only. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period. Some examples of soft food or liquids include pureed fruits or vegetables, yogurt, applesauce, water, milk, or juice. A fat-containing meal or snack should be consumed just before or after dosing.

Dosage adjustment

Hepatic impairment

Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, TRIKAFTA should be used with caution at a reduced dose (see Table 2).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with TRIKAFTA.

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and 5.2 PHARMACOKINETIC PROPERTIES).

Table 2: Recommendation for Use in Patients with Hepatic Impairment

Age	Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
2 to < 6 years	No dose adjustment	**Use not recommended.** Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, TRIKAFTA should be used with caution at a reduced dose, as follows: • Days 1-3: one sachet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 4: no dose • Days 5-6: one sachet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 7: no dose Repeat above dosing schedule each week. The evening dose of ivacaftor granules should not be taken.	Should not be used
6 years and older	No dose adjustment	**Use not recommended.** Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, TRIKAFTA should be used with caution at a reduced dose, as follows:	Should not be used

Table 2: Recommendation for Use in Patients with Hepatic Impairment			
Age	**Mild (Child-Pugh Class A)**	**Moderate (Child-Pugh Class B)**	**Severe (Child-Pugh Class C)**
		• Day 1: two elexacaftor/tezacaftor/ivacaftor tablets in the morning • Day 2: one elexacaftor/tezacaftor/ivacaftor tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. The evening dose of the ivacaftor tablet should not be taken.	

Renal impairment
No dose adjustment is recommended for patients with mild and moderate renal impairment. Caution is recommended for patients with severe renal impairment or end-stage renal disease (see section 5.2 PHARMACOKINETIC PROPERTIES).

Concomitant use of CYP3A inhibitors
When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin, verapamil) or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dose should be reduced as in Table 3 (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 3: Dosing Schedule for Concomitant Use of TRIKAFTA with Moderate and Strong CYP3A Inhibitors						
Moderate CYP3A Inhibitors						
			Day 1	**Day 2**	**Day 3**	**Day 4***
2 to <6 years	**Morning Dose**	One elexacaftor/tezacaftor/ivacaftor granules sachet	✓	-	✓	-
		One ivacaftor granules sachet	-	✓	-	✓
	Evening Dose^	One ivacaftor granules sachet	No dose			
6 years and older	**Morning Dose**	Two elexacaftor/tezacaftor/ivacaftor tablets	✓	-	✓	-
		One ivacaftor tablet	-	✓	-	✓
	Evening Dose^	One ivacaftor tablet	No dose			
* Continue dosing with elexacaftor/tezacaftor/ivacaftor tablets or sachets and ivacaftor tablets or sachets on alternate days. ^ The evening dose of ivacaftor should not be taken.						
Strong CYP3A Inhibitors						
			Day 1	**Day 2 and Day 3**		**Day 4#**

2 to <6 years	**Morning Dose**	One elexacaftor/ tezacaftor/ ivacaftor granules sachet	✓	-	✓
	Evening Dose^	One ivacaftor granules sachet	No dose		
6 years and older	**Morning Dose**	Two elexacaftor/ tezacaftor/ivacaftor tablets	✓	-	✓
	Evening Dose^	One ivacaftor tablet	No dose		
# Continue dosing with elexacaftor/tezacaftor/ivacaftor tablets or sachets twice a week, approximately 3 to 4 days apart. ^ The evening dose of ivacaftor should not be taken.					

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

Use in hepatic impairment
Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with TRIKAFTA. Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. For patients with moderate hepatic impairment, TRIKAFTA should only be used if there is a clear medical need, and the benefits are expected to outweigh the risks. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES).

Elevated transaminases and hepatic injury
Cases of liver failure leading to transplantation have been reported within the first 6 months of treatment in patients with and without pre-existing advanced liver disease.

Elevated transaminases are common in patients with CF and have been observed in patients treated with TRIKAFTA. In some instances, these elevations have been associated with concomitant elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating TRIKAFTA, every month during the first 6 months of treatment, every 3 months during the next 6 months and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt TRIKAFTA and promptly measure serum transaminases and total bilirubin if a patient develops clinical signs or symptoms suggestive of liver injury (e.g. jaundice and/or dark urine, unexplained nausea or vomiting, right upper quadrant pain, or anorexia). Interrupt dosing in the event of ALT or AST > 5 x the upper limit of normal (ULN), or ALT or AST > 3 x ULN with total bilirubin > 2 x ULN. Follow laboratory tests closely until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and 5.2 PHARMACOKINETIC PROPERTIES). Patients who resume treatment after interruption should be monitored closely.

In patients with pre-existing advanced liver disease (e.g. cirrhosis, portal hypertension), TRIKAFTA should be used with caution and only if the benefits are expected to outweigh the

risks (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), and 5.2 PHARMACOKINETIC PROPERTIES).

Interactions with medicinal products

CYP3A inducers

Exposure to ivacaftor is significantly decreased and exposures to elexacaftor and tezacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduction of TRIKAFTA efficacy; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

CYP3A inhibitors

Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose of TRIKAFTA should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Table 3 in section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 TRIKAFTA and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with TRIKAFTA.

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation) a possible risk attributable to treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with TRIKAFTA. 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 systemic exposure in animals approximately 5 times lower than that in patients at the maximum recommended human dose [MRHD] based on summed AUCs of the ivacaftor component of TRIKAFTA and its major metabolites). This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

Effects on laboratory tests

Refer to section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Elevated transaminases and hepatic injury.

Patients after organ transplantation

TRIKAFTA 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, everolimus, sirolimus or tacrolimus).

Use in the elderly

Clinical trials of TRIKAFTA did not include a sufficient number of patients aged 65 years and older to determine whether they respond differently from younger patients.

Paediatric use
The safety and efficacy of TRIKAFTA in children aged less than 2 years have not been established (see sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products affecting the pharmacokinetics of TRIKAFTA
CYP3A inducers
Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced TRIKAFTA efficacy. Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor exposures are expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration of TRIKAFTA with strong CYP3A inducers is not recommended (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Examples of strong CYP3A inducers include:
- rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

CYP3A inhibitors
Co-administration with itraconazole, a strong CYP3A inhibitor, increased elexacaftor AUC by 2.8-fold and tezacaftor AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, ivacaftor AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of TRIKAFTA should be reduced when co-administered with strong CYP3A inhibitors (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Table 3 in section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9- to 2.3-fold. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dose of TRIKAFTA should be reduced when co-administered with moderate CYP3A inhibitors (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Table 3 in section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Examples of moderate CYP3A inhibitors include:
- fluconazole
- erythromycin
- verapamil

Co-administration of TRIKAFTA with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor and ivacaftor. Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 4 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Table 4: Impact of Other Drugs on Elexacaftor, Tezacaftor and Ivacaftor				
Dose and Schedule		**Effect on ELX, TEZ and/or IVA PK**	**Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0**	
			AUC	**C_{max}**
Itraconazole 200 mg q12h on Day 1, followed by 200 mg qd	tezacaftor 25 mg qd + ivacaftor 50 mg qd	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
		↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Itraconazole 200 mg qd	elexacaftor 20 mg + tezacaftor 50 mg single dose	↑ Elexacaftor	2.83 (2.59, 3.10)	1.05 (0.977, 1.13)
		↑ Tezacaftor	4.51 (3.85, 5.29)	1.48 (1.33, 1.65)
Ketoconazole 400 mg qd	ivacaftor 150 mg single dose	↑ Ivacaftor	8.45 (7.14, 10.0)	2.65 (2.21, 3.18)
Ciprofloxacin 750 mg q12h	tezacaftor 50 mg q12h + ivacaftor 150 mg q12h	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
		↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)
Rifampicin 600 mg qd	ivacaftor 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole 400 mg single dose on Day 1, followed by 200 mg qd	ivacaftor 150 mg q12h	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)
↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence Interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics * Effect is not clinically significant.				

Medicinal products affected by TRIKAFTA

CYP2C9 substrates

Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalised ratio (INR) during co-administration of TRIKAFTA with warfarin is recommended. Other medicinal products for which exposure may be increased by TRIKAFTA include glimepiride and glipizide; these medicinal products should be used with caution.

Potential for interaction with transporters

Co-administration of ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive P-glycoprotein (P-gp) substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of TRIKAFTA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as ciclosporin, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

Elexacaftor and M23-ELX (active metabolite) inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Tezacaftor/ivacaftor increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration of TRIKAFTA may increase exposures of medicinal products that are substrates of these transporters, such as statins, glyburide, nateglinide and repaglinide. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used. Bilirubin is an OATP1B1 and OATP1B3 substrate. In Study 445-102, mild

increases in mean total bilirubin were observed (up to 4.0 µmol/L change from baseline). This finding is consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by elexacaftor and M23-ELX.

Hormonal contraceptives
TRIKAFTA has been studied with ethinyl estradiol/levonorgestrel and was found to have no clinically relevant effect on the exposures of the oral contraceptive. TRIKAFTA is not expected to have an impact on the efficacy of oral contraceptives.

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 5.

Table 5: Impact of Elexacaftor, Tezacaftor and Ivacaftor on Other Drugs

Dose and Schedule		**Effect on Other Drug PK**	**Geometric Mean Ratio (90% CI) of Other Drug No Effect=1.0**	
			AUC	**C_{max}**
Midazolam 2 mg single oral dose	TEZ 100 mg qd/IVA 150 mg q12h	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin 0.5 mg single dose	TEZ 100 mg qd/IVA 150 mg q12h	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd	ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	↑ Ethinyl estradiol* ↑ Levonorgestrel*	1.33 (1.20, 1.49) 1.23 (1.10, 1.37)	1.26 (1.14, 1.39) 1.10 (0.985, 1.23)
Rosiglitazone 4 mg single oral dose	IVA 150 mg q12h	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine 50 mg single dose	IVA 150 mg q12h	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939, 1.07)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence Interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
* Effect is not clinically significant (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data available on the effect of elexacaftor, tezacaftor, and ivacaftor on fertility in humans.

Elexacaftor impaired male and female fertility in rats at oral doses of 75 mg/kg/day and 35 mg/kg/day in the respective sexes (yielding systemic exposure in animals approximately 6 and 7 times greater, respectively, than that in patients at the MRHD based on summed AUCs of the elexacaftor component of TRIKAFTA and its major active metabolite, M23-ELX).

Tezacaftor did not affect fertility or reproductive performance indices in male and female rats at oral doses up to 100 mg/kg/day (yielding systemic exposure in animals approximately 3 times greater than that in patients at the MRHD based on summed AUCs of the tezacaftor component of TRIKAFTA and its pharmacologically active metabolite, M1-TEZ).

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding systemic exposure in animals approximately 10 and 5 times greater, respectively, than that in patients at the MRHD based on summed AUCs of the ivacaftor component of TRIKAFTA 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 systemic exposure in animals approximately 5 and 3 times greater, respectively, than that in patients at the MRHD based on the summed AUCs of the ivacaftor component of TRIKAFTA and its major metabolites).

Use in pregnancy
Category B3
Category B3 drugs have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Elexacaftor, tezacaftor, ivacaftor and/or their metabolites were shown to cross the placenta in laboratory animal species (rats and/or rabbits).

Elexacaftor
Elexacaftor was not teratogenic in rats at oral doses up to 40 mg/kg/day or up to 125 mg/kg/day in rabbits (yielding systemic exposure in animals approximately 9 and 4 times greater, respectively, than that in patients at the MRHD based on summed AUCs of the elexacaftor component of TRIKAFTA and M23-ELX [for rat], or AUC of the elexacaftor component of TRIKAFTA [for rabbit]). Effects on embryofetal development were limited to lower mean fetal body weight (at ≥ 25 mg/kg/day). Pup birth and postnatal body weights were reduced in rats with maternal treatment at 10 mg/kg/day during gestation and lactation.

Tezacaftor
No evidence of harm to the fetus was observed with tezacaftor in developmental toxicity study in rats at oral doses up to 100 mg/kg/day (yielding systemic exposure in animals approximately 3 times greater than that in patients at the MRHD based on summed AUCs of the tezacaftor component of TRIKAFTA and its pharmacologically active M1 metabolite, M1-TEZ). In the rabbit, lower fetal body weights were noted at an oral dose of 50 mg/kg/day (the highest dose tested; yielding exposure around the same as at the MRHD), which occurred in conjunction with significant maternal toxicity. However, no effects on embryo fetal survival and no malformations were observed with tezacaftor in the species. Fetal body weight was unaffected in rabbits at 25 mg/kg/day (yielding exposure 4 times lower than that at the MRHD based on summed AUCs of tezacaftor and its M1 metabolite).

Ivacaftor
Developmental toxicity studies with ivacaftor revealed no teratogenicity in rats at oral doses up to 200 mg/kg/day or rabbits at oral doses up to 100 mg/kg/day (yielding systemic exposure in the respective animal species approximately 5 and≥ 3 times greater, than that in patients at the MRHD based on summed AUCs of the ivacaftor component of TRIKAFTA and its major metabolites). 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.

No adequate and well-controlled studies of TRIKAFTA in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, TRIKAFTA should be used during pregnancy only if the potential benefits outweigh the potential risks.

Use in lactation
Elexacaftor, tezacaftor and ivacaftor are excreted into the milk of lactating female rats. Exposure of ^{14}C-elexacaftor, ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 0.4, 2.1, and 1.5 times respectively, the value observed in plasma (based on $AUC_{0\text{-}24}$h). Because it is not known if elexacaftor, tezacaftor, ivacaftor, or their metabolites are excreted in human milk, TRIKAFTA should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile
The safety profile of TRIKAFTA is based on data from 510 patients in two double-blind, controlled, phase 3 studies of 24 weeks and 4 weeks treatment duration (Studies 445-102 and 445-103). In the two controlled phase 3 studies, a total of 257 patients aged 12 years and older received at least one dose of TRIKAFTA.

In Study 445-102, the proportion of patients who discontinued study drug prematurely due to adverse events was 1% for TRIKAFTA-treated patients and 0% for placebo-treated patients.

Serious adverse drug reactions that occurred more frequently in TRIKAFTA-treated patients compared to placebo were rash events in 3 (1.5%) TRIKAFTA-treated patients vs. 1 (0.5%) placebo. The most common (≥ 10%) adverse drug reactions in patients treated with TRIKAFTA were headache, diarrhoea and upper respiratory tract infection.

The safety profile of TRIKAFTA was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$), and geographic regions.

Table 6 shows adverse events with an incidence of at least 10% in any treatment group from the double-blind, placebo-controlled, phase 3 clinical Study 445-102 (24 weeks duration).

Table 6: Adverse Events with an Incidence of at Least 10% in Any Treatment Group of Patients Aged 12 Years and Older who were Heterozygous for the *F508del* Mutation in the *CFTR* Gene

Preferred Term	TRIKAFTA N=202 n (%)	Placebo N=201 n (%)
Infective pulmonary exacerbation of cystic fibrosis	44 (21.8)	95 (47.3)
Sputum increased	40 (19.8)	39 (19.4)
Headache	35 (17.3)	30 (14.9)
Cough	34 (16.8)	77 (38.3)
Diarrhoea	26 (12.9)	14 (7.0)
Upper respiratory tract infection	24 (11.9)	22 (10.9)
Nasopharyngitis	22 (10.9)	26 (12.9)

Rash	21 (10)	10 (5)*
Oropharyngeal pain	20 (9.9)	25 (12.4)
Haemoptysis	11 (5.4)	28 (13.9)
Fatigue	9 (4.5)	20 (10.0)
*Includes rash, rash generalised, rash erythematous, rash macular, rash pruritic		

Tabulated list of adverse reactions

Table 7 shows adverse drug events occurring in ≥ 8% of TRIKAFTA-treated patients and at a frequency higher than placebo by ≥ 1% in Study 445-102. Adverse drug events for TRIKAFTA 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).

Table 7: Adverse Drug Reactions by Preferred Term, Incidence and Frequency

System Organ Class (SOC)	Adverse Drug Reactions (Preferred Term)	TRIKAFTA N=202 n (%)	Placebo N=201 n (%)	Frequency for TRIKAFTA
Infections and infestations	Upper respiratory tract infection	24 (11.9)	22 (10.9)	very common
Nervous system disorders	Headache	35 (17.3)	30 (14.9)	very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	19 (9.4)	15 (7.5)	common
	Rhinorrhoea	17 (8.4)	6 (3.0)	common
Gastrointestinal disorders	Diarrhoea	26 (12.9)	14 (7.0)	very common
	Abdominal pain	20 (9.9)	12 (6.0)	common
Skin and subcutaneous tissue disorders	Rash	21 (10)	10 (5)	very common*
Investigations	Alanine aminotransferase increased	20 (9.9)	7 (3.5)	common
	Aspartate aminotransferase increased	19 (9.4)	4 (2.0)	common
	Blood creatine phosphokinase increased	19 (9.4)	9 (4.5)	common
*Includes rash, rash generalised, rash erythematous, rash macular, rash pruritic				

Safety data from the following studies were consistent with the safety data observed in Study 445-102.

- A 4-week, randomised, double-blind, active-controlled study in 107 patients (Study 445-103).
- A 192-week, open-label safety and efficacy study (Study 445-105) for patients rolled over from Studies 445-102 and 445-103.
- An 8-week, randomised, double-blind, active-controlled study in 258 patients (Study 445-104).
- A 24-week, open-label study (Study 445-106) in 66 patients aged 6 to less than 12 years.
- A 24-week, open-label study (Study 445-111) in 75 patients aged 2 to less than 6 years.

- A 192-week, two-part (part A and part B), open-label safety and efficacy study (Study 445-107) in patients aged 6 years and older who rolled over from Study 445-106, with Part A analysis (96 weeks) performed on 64 patients.
- A 24-week, randomised, double-blind, placebo-controlled study (Study 445-124) in 307 patients aged 6 years and older.

Detailed description of selected adverse events

Laboratory abnormalities

Transaminase elevations

In Study 445-102, the incidence of maximum transaminase (ALT or AST) > 8, > 5, or > 3 x the ULN was 1.5%, 2.5%, and 7.9% in TRIKAFTA-treated patients and 1.0%, 1.5%, and 5.5% in placebo-treated patients. The incidence of adverse reactions of transaminase elevations was 10.9% in TRIKAFTA-treated patients and 4.0% in placebo-treated patients. No TRIKAFTA-treated patients discontinued treatment for elevated transaminases (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

During Study 445-106 in patients aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) > 8, > 5, and > 3 x ULN were 0%, 1.5%, and 10.6%, respectively. No TRIKAFTA-treated patients had transaminase elevation > 3 x ULN associated with elevated total bilirubin > 2 x ULN or discontinued treatment due to transaminase elevations (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

During Study 445-111 in patients aged 2 to less than 6 years, the incidence of maximum transaminase (ALT or AST) > 8, > 5, and > 3 x ULN were 1.3%, 2.7%, and 8.0%, respectively. No TRIKAFTA-treated patients had transaminase elevation > 3 x ULN associated with elevated total bilirubin > 2 x ULN or discontinued treatment due to transaminase elevations (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Rash events

Studies in TRIKAFTA-treated patients above 12 years of age showed an incidence of rash events (e.g., rash, rash pruritic) of 10.9% (study 445-102) compared to 6.5% in placebo-treated patients. The paediatric population showed a higher incidence rate (see section Paediatric population for further details). The incidence of rash events by patient sex was 5.8% in males and 16.3% in females in TRIKAFTA-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients. In patients treated with TRIKAFTA, the incidence of rash events was 20.5% in females taking hormonal contraceptive and 13.6% in females not taking hormonal contraceptive (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Overall, rash events typically occur during the first month of therapy. Most events were mild to moderate in severity, and in rare cases, rash was associated with additional symptoms such as fever or facial swelling. In the majority of cases, administration of TRIKAFTA was continued and the rash resolved without treatment.

A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, consider interrupting TRIKAFTA and hormonal contraceptives. Following the resolution of rash, consider resuming TRIKAFTA without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.

Paediatric Population

Rash

While studies in patients above 12 years of age showed an incidence rate of 10.9% (study 445-102), patients between 6 and 11 years of age had an incidence rate of 24.2% (study 445-106). During study 445-111 in patients aged 2 to less than 6 years, 15 (20.0%) subjects had at least 1 rash event, 4 (9.8%) females and 11 (32.4%) males.

Increased creatine phosphokinase

In Study 445-102, the incidence of maximum creatine phosphokinase > 5 x the ULN was 10.4% in TRIKAFTA-treated patients and 5.0% in placebo-treated patients. No TRIKAFTA-treated patients discontinued treatment for increased creatine phosphokinase.

In Study 445-111 CK elevation occurred in 1 (1.3%) subject. The mean (SD) increase in CK ranged from 25.7 (82.4) U/L at Day 15 to 41.7 (47.3) U/L at Week 20. The majority of subjects had CK levels ≤2 × ULN; no subjects had CK levels >5 x ULN.

Increased blood pressure

In Study 445-102, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for TRIKAFTA-treated patients (baseline: 113 mmHg systolic and 69 mmHg diastolic) and 0.9 mmHg and 0.5 mmHg, respectively for placebo-treated patients (baseline: 114 mmHg systolic and 70 mmHg diastolic).

The proportion of patients who had systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg on at least two occasions was 5.0% and 3.0% in TRIKAFTA-treated patients respectively, compared with 3.5% and 3.5% in placebo-treated patients, respectively.

Post-marketing experience

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

Liver failure leading to transplantation in patients with and without pre-existing advanced liver disease (e.g. cirrhosis, portal hypertension). Liver injury characterised by concomitant transaminase (ALT and AST) and total bilirubin elevations (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune system disorders:

- Anaphylaxis
- Hypersensitivity.

Reporting suspected adverse effects

Reporting of 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

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Respiratory system, Other respiratory system products; ATC code: R07AX32

Mechanism of action
Elexacaftor and tezacaftor are CFTR correctors that bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. (see *Clinical efficacy*).

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR.

The chloride transport response of mutant CFTR protein to ELX/TEZ/IVA was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. ELX/TEZ/IVA increased chloride transport in FRT cells expressing select *CFTR* mutations.

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

Clinical outcomes were consistent with *in vitro* results and indicate that a single elexacaftor/tezacaftor/ivacaftor responsive mutation is sufficient to result in a significant clinical response (see *Clinical efficacy*).

Table 8 lists responsive CFTR mutations based on clinical response and/or *in vitro* data in FRT cells indicating that elexacaftor/tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline.

Table 8: List of CFTR Gene Mutations Responsive to TRIKAFTA				
Mutations responsive to TRIKAFTA based on clinical data*				
2789+5G→A	*D1152H†*	*L206W†*	*R1066H†*	*S945L†*
3272-26A→G	*F508del†*	*L997F†*	*R117C†*	*T338I†*

3849+10kbC→T	*G85E*†	*M1101K*†	*R347H*†	*V232D*†
A455E†	*L1077P*†	*P5L*†	*R347P*†	
Mutations responsive to TRIKAFTA based on in vitro data‡				
1507_1515del9	*F311L*	*I1366N*	*Q1291R*	*S1159P*
2183A→G	*F508C*	*I148N*	*Q1313K*	*S1235R*
3141del9	*F508C;S1251N*	*I148T*	*Q237E*	*S1251N*
546insCTA	*F575Y*	*I175V*	*Q237H*	*S1255P*
A1006E	*F587I*	*I331N*	*Q359R*	*S13F*
A1067P	*G1047R*	*I336K*	*Q372H*	*S341P*
A1067T	*G1061R*	*I502T*	*Q493R*	*S364P*
A107G	*G1069R*	*I506L*	*Q552P*	*S492F*
A120T	*G1123R*	*I556V*	*Q98R*	*S549I*
A234D	*G1244E*	*I601F*	*R1048G*	*S549N*
A309D	*G1247R*	*I618T*	*R1070Q*	*S549R*
A349V	*G1249R*	*I807M*	*R1070W*	*S589N*
A46D	*G126D*	*I980K*	*R1162L*	*S737F*
A554E	*G1349D*	*K1060T*	*R117C;G576A;R668C*	*S912L*
A62P	*G178E*	*K162E*	*R117G*	*S977F*
C491R	*G178R*	*K464E*	*R117H*	*T1036N*
D110E	*G194R*	*L1011S*	*R117L*	*T1053I*
D110H	*G194V*	*L1324P*	*R117P*	*T1086I*
D1270N	*G27E*	*L1335P*	*R1283M*	*T1246I*
D1445N	*G27R*	*L137P*	*R1283S*	*T1299I*
D192G	*G314E*	*L1480P*	*R170H*	*T351I*
D443Y	*G424S*	*L15P*	*R258G*	*V1153E*
D443Y;G576A;R668C	*G463V*	*L165S*	*R297Q*	*V1240G*
D565G	*G480C*	*L320V*	*R31C*	*V1293G*
D579G	*G480S*	*L333F*	*R31L*	*V201M*
D614G	*G551A*	*L333H*	*R334L*	*V392G*
D836Y	*G551D*	*L346P*	*R334Q*	*V456A*

D924N	*G551S*	*L441P*	*R347L*	*V456F*
D979V	*G576A*	*L453S*	*R352Q*	*V562I*
D993Y	*G576A;R668C*	*L619S*	*R352W*	*V603F*
E116K	*G622D*	*L967S*	*R516S*	*V754M*
E116Q	*G628R*	*M1137V*	*R553Q*	*W1098C*
E193K	*G970D*	*M150K*	*R555G*	*W1282R*
E292K	*G970S*	*M152V*	*R668C*	*W361R*
E403D	*H1054D*	*M265R*	*R709Q*	*Y1014C*
E474K	*H1085P*	*M952I*	*R74Q*	*Y1032C*
E56K	*H1085R*	*M952T*	*R74W*	*Y109N*
E588V	*H1375P*	*N1088D*	*R74W;D1270N*	*Y161D*
E60K	*H139R*	*N1303I*	*R74W;V201M*	*Y161S*
E822K	*H199Y*	*N1303K*	*R74W;V201M;D1270N*	*Y301C*
E92K	*H620P*	*N186K*	*R751L*	*Y563N*
F1016S	*H620Q*	*N187K*	*R75L*	
F1052V	*H939R*	*N418S*	*R75Q*	
F1074L	*H939R;H949L*	*P140S*	*R792G*	
F1099L	*I1027T*	*P205S*	*R933G*	
F1107L	*I105N*	*P499A*	*S1045Y*	
F191V	*I1139V*	*P574H*	*S108F*	
F200I	*I125T*	*P67L*	*S1118F*	
F311del	*I1269N*	*P750L*	*S1159F*	
Mutations responsive to TRIKAFTA based on extrapolation from Trial 5[§]				
4005+2T→C	*2789+2insA*	*3849+40A→G*	*5T;TG13*	
1341G→A	*296+28A→G*	*3849+4A→G*	*621+3A→G*	
1898+3A→G	*3041-15T→G*	*3850-3T→G*	*711+3A→G*	
2752-26A→G	*3600G→A*	*5T;TG12*	*E831X*	

There may be patients with mutations not listed in Table 8. Provided they do not harbour two Class I mutations, TRIKAFTA can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision.

* Clinical data obtained from Trials 445-102, 445-103, and 445-124.

† This mutation is also predicted to be responsive by FRT assay.

ǂ The N1303K mutation is predicted to be responsive by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.

§ Efficacy is extrapolated from Trial 445-124 to non-canonical splice mutations because clinical trials in all mutations of this subgroup are infeasible, and these mutations are not amenable to interrogation by FRT system.

Clinical trials

Pharmacodynamic effects

Effects on sweat chloride

In Study 445-102 (patients with an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor [minimal function mutation]), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period. The treatment difference of TRIKAFTA compared to placebo for mean absolute change in sweat chloride from baseline through Week 24 was -41.8 mmol/L (95% CI: -44.4, -39.3; *P*<0.0001).

In Study 445-103 (patients homozygous for the *F508del* mutation), the treatment difference of TRIKAFTA compared to tezacaftor/ivacaftor for mean absolute change in sweat chloride from baseline at Week 4 was -45.1 mmol/L (95% CI: -50.1, -40.1; *P*<0.0001).

In Study 445-104 (patients heterozygous for the *F508del* mutation and a gating or residual function mutation on the second allele), following a 4-week ivacaftor or tezacaftor/ivacaftor run-in period, the mean absolute change in sweat chloride from baseline through Week 8 for the TRIKAFTA group was -22.3 mmol/L (95% CI: -24.5, -20.2; *P*<0.0001). The treatment difference of TRIKAFTA compared to the control group (ivacaftor or tezacaftor/ivacaftor) was -23.1 mmol/L (95% CI: -26.1, -20.1; *P*<0.0001).

In Study 445-106 (patients aged 6 to less than 12 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2).

In Study 445-111 (patients aged 2 to less than 6 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -57.9 mmol/L (95% CI: -61.3, -54.6).

In Study 445-124 (patients aged 6 years and older with a qualifying non-*F508del,* ELX/TEZ/IVA-responsive mutation [see Table 15]), the mean absolute change in sweat chloride from baseline through Week 24 compared to placebo was -28.3 mmol/L (95% CI:-32.1, -24.5 mmol/L; P <0.0001).

Cardiovascular effects

Effect on QT interval

At doses up to 2 times the maximum recommended dose of elexacaftor and 3 times the maximum recommended dose of tezacaftor and ivacaftor, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Heart rate

In Study 445-102, mean decreases in heart rate of 3.7 to 5.8 beats per minute (bpm) from baseline (76 bpm) were observed in TRIKAFTA-treated patients.

Clinical efficacy

The efficacy of TRIKAFTA in patients with CF was demonstrated in four phase 3, double-blind, controlled studies (Studies 445-102, 445-103, 445-104 and 445-124), a phase 3 open-label extension study (Study 445-105), and two phase 3 open-label studies (Study 445-106 and Study 445-111). These studies enrolled CF patients with at least one *F508del* mutation or a mutation responsive to TRIKAFTA listed in Table 8. Significant clinical benefit was demonstrated in all studies.

Patients in Studies 445-102, 445-103, 445-104, 445-106, 445-111 and 445-124 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies, except for study drugs. Patients had a confirmed diagnosis of CF and at least one *F508del* mutation or a mutation responsive based on clinical or in vitro evidence.

Patients in Studies 445-102, 445-103, 445-104, 445-106, 445-111 and 445-124 who had lung infection with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT≥ 3 x ULN, or total bilirubin≥ 2 x ULN), were excluded. In Study 445-111, patients who had ALT or AST ≥ 2 x ULN were also excluded.

Patients in Studies 445-102 and 445-103 were eligible to roll over into a 192-week open-label extension study (Study 445-105). Patients in Studies 445-104, 445-106, 445-111 and 445-124 were eligible to roll over into distinct open-label extension studies.

***Study 445-102**: **S**tudy in patients who had an **F508del** mutation on one allele and a mutation on the second allele that results in either no CFTR / non-responsive CFTR protein.*

Study 445-102 was a 24-week, randomised, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and a minimal function mutation on the second allele. * A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomised and dosed to receive TRIKAFTA or placebo. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%).
*Contact sponsor (see section 8 SPONSOR) for list of mutations enrolled in Study 445-102.

In Study 445-102 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through Week 24. Treatment with TRIKAFTA compared to placebo resulted in statistically significant improvement in $ppFEV_1$ of 14.3 percentage points (95% CI: 12.7, 15.8; P<0.0001) (see Table 9). Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained through the 24-week treatment period (see Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region. A total of 18 patients receiving TRIKAFTA had $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population. See Table 9 for a summary of primary and key secondary outcomes.

Table 9: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102)			
Analysis	**Statistic**	**Placebo N=203**	**TRIKAFTA N=200**
Primary			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.5)	14.3 (12.7, 15.8) *P*<0.0001 13.9 (0.6)
Key Secondary			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.2 (0.6)	13.7 (12.0, 15.3) *P*<0.0001 13.5 (0.6)
Number of pulmonary exacerbations from baseline through Week 24‡	Number of events (event rate per year††) Rate ratio (95% CI) *P* value	113 (0.98) NA NA	41 (0.37) 0.37 (0.25, 0.55) *P*<0.0001
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.9)	-41.8 (-44.4, -39.3) *P*<0.0001 -42.2 (0.9)
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.7 (1.0)	20.2 (17.5, 23.0) *P*<0.0001 17.5 (1.0)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.09 (0.07)	1.04 (0.85, 1.23) *P*<0.0001 1.13 (0.07)
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.1 (1.0)	-41.2 (-44.0, -38.5) *P*<0.0001 -41.2 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.9 (1.1)	20.1 (16.9, 23.2) *P*<0.0001 18.1 (1.1)
$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SE: Standard Error; NA: Not Applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: Body Mass Index. ‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. †† Estimated event rate per year was calculated based on 48 weeks per year.			

At Week 24 the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with TRIKAFTA compared with placebo. The rate ratio of exacerbations through Week 24 in patients treated with TRIKAFTA was 0.37 (95% CI: 0.25, 0.55; *P*<0.0001), representing a reduction relative to placebo of 63% (see Figure 2).

Figure 1: Absolute Change from Baseline in Percent Predicted FEV_1 at Each Visit in Study 445-102

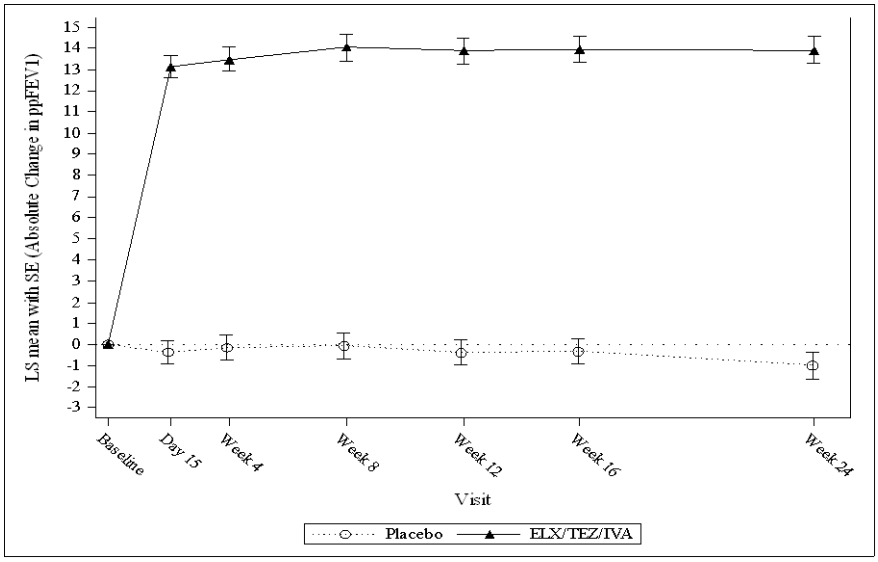
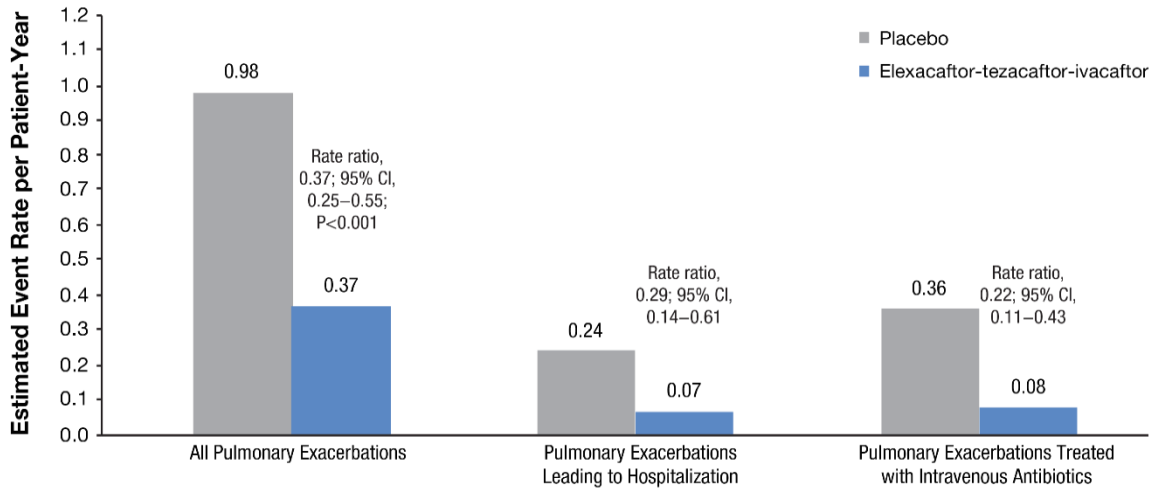


Figure 2: Pulmonary Exacerbations at Week 24 in Study 445-102 –
Overall estimated annualised rate of pulmonary exacerbations (key secondary endpoint), the estimated annualised rate of pulmonary exacerbations leading to hospitalization, and the estimated annualised rate of pulmonary exacerbations treated with intravenous antibiotics. CI denotes confidence interval.



Study 445-103: *S*tudy in patients who are homozygous for the *F508del* mutation and randomised to TRIKAFTA or SYMDEKO tablets.
Study 445-103 was a 4-week, randomised, double-blind, active-controlled study in patients who are homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received SYMDEKO (tezacaftor/ivacaftor and ivacaftor regimen) during a 4-week open-label run-in period and were then randomised and dosed to receive TRIKAFTA or SYMDEKO during a 4-week double-blind treatment period. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline, following the SYMDEKO run-in period was 60.9% (range: 35.0%, 89.0%).

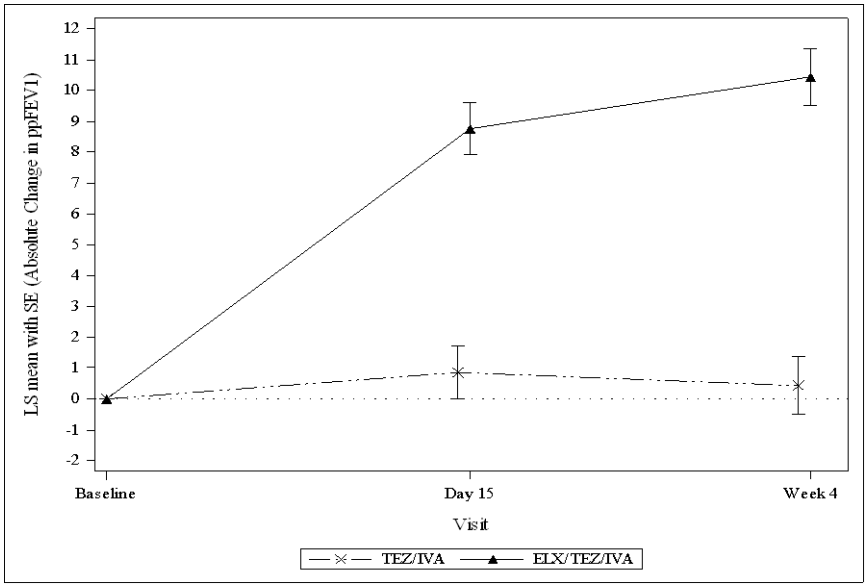
In Study 445-103 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. Treatment with TRIKAFTA compared to the SYMDEKO resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; *P*<0.0001) (see Table 10). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region. See Table 10 for a summary of primary and key secondary outcomes.

Table 10: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-103)

Analysis*	Statistic	SYMDEKO N=52	TRIKAFTA N=55
Primary			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.4 (0.9)	10.0 (7.4, 12.6) *P*<0.0001 10.4 (0.9)
Key Secondary			
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.7 (1.8)	-45.1 (-50.1, -40.1) *P*<0.0001 -43.4 (1.7)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.4 (2.0)	17.4 (11.8, 23.0) *P*<0.0001 16.0 (2.0)

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SE: Standard Error; NA: Not Applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised.
*Baseline for primary and key secondary endpoints is defined as the end of the 4-week run-in period of SYMDEKO.

Figure 3: Absolute Change from Baseline in Percent Predicted FEV_1 at Each Visit in Study 445-103.



***Study 445-104*: Study in patients aged 12 years and older who are heterozygous for the *F508del* mutation and a gating or residual function mutation.**

Study 445-104 was an 8-week, randomised, double-blind, active-controlled study in patients who were heterozygous for the *F508del* mutation and a gating or residual function (RF) mutation on the second allele. A total of 258 patients aged 12 years and older received either KALYDECO (for F/G patients) or SYMDEKO (for F/RF patients) during a 4-week open-label run-in period and were dosed during the treatment period. Patients with the *F/R117H* genotype received ivacaftor during the run-in period. The mean age at baseline, following the run-in period was 37.7 years. Patients were then randomised to the TRIKAFTA group or remained on the CFTR modulator therapy received during the run-in period. Patients had a $ppFEV_1$ screening between 40-90%. The mean $ppFEV_1$ at baseline was 67.6% (range: 29.7%, 113.5%).

Following a 4-week KALYDECO or SYMDEKO run-in period, the primary endpoint of within-group mean absolute change in $ppFEV_1$ from baseline through Week 8 for the TRIKAFTA group resulted in statistically significant improvement in $ppFEV_1$ of 3.7 percentage points (95% CI: 2.8, 4.6; $P<0.0001$) (see Table 11). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15. Overall improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ geographic region, and genotype groups (F/G or F/RF).

See Table 11 for a summary of primary and secondary outcomes in the overall trial population.

In a subgroup analysis of patients with an F/G genotype, the treatment difference of TRIKAFTA (N=50) compared with KALYDECO(N=45) for mean absolute change in $ppFEV_1$ was 5.8 percentage points (95% CI: 3.5, 8.0). In a subgroup analysis of patients with an F/RF genotype, the treatment difference of TRIKAFTA (N=82) compared with SYMDEKO(N=81) for mean absolute change in $ppFEV_1$ was 2.0 percentage points (95% CI: 0.5, 3.4). The results of the F/G

and the F/RF genotype subgroups for improvement in sweat chloride and CFQ-R respiratory domain score were consistent with the overall results.

Table 11: Primary and Secondary Efficacy Analyses, Full Analysis Set (Study 445-104)

Analysis*	Statistic	Control Group# N=126	TRIKAFTA N=132
Primary			
Absolute change in ppFEV$_1$ from baseline through Week 8 (percentage points)	Within-group change (95% CI) *P* value	0.2 (-0.7, 1.1) NA	3.7 (2.8, 4.6) *P*<0.0001
Key and Other Secondary			
Absolute change in sweat chloride from baseline through Week 8 (mmol/L)	Within-group change (95% CI) *P* value	0.7 (-1.4, 2.8) NA	-22.3 (-24.5, -20.2) *P*<0.0001
Absolute change in ppFEV$_1$ from baseline through Week 8 compared to the control group (percentage points)	Treatment difference (95% CI) *P* value	NA NA	3.5 (2.2, 4.7) *P*<0.0001
Absolute change in sweat chloride from baseline through Week 8 compared to the control group (mmol/L)	Treatment difference (95% CI) *P* value	NA NA	-23.1 (-26.1, -20.1) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline through Week 8 (points)	Within-group change (95% CI)	1.6 (-0.8, 4.1)	10.3 (8.0, 12.7)
Absolute change in CFQ-R respiratory domain score from baseline through Week 8 compared to the control group (points)	Treatment difference (95% CI)	NA	8.7 (5.3, 12.1)

ppFEV$_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; NA: Not Applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised.
* Baseline for primary and secondary endpoints is defined as the end of the 4-week run-in period of KALYDECO or SYMDEKO.
# KALYDECO group or SYMDEKO group.

Study 445-105: A 192 week open-label study in patients aged 12 years and older rolled over from Studies 445-102 and 445-103.
Study 445-105 was a 192-week open-label extension study to evaluate the safety and efficacy of long-term treatment with TRIKAFTA conducted in patients who rolled over from Studies 445-102 (N=400) and 445-103 (N=107). In this open-label extension study, all patients received TRIKAFTA for the duration of the study

In Study 445-105, patients from the control arms in the parent studies showed improvements in efficacy endpoints consistent with those observed in subjects who received TRIKAFTA in the parent studies. Patients from the control arms as well as patients who received TRIKAFTA in the parent studies showed sustained improvements in ppFEV$_1$ (see Figure 4 and Figure 5) and other efficacy endpoints (see Table 12).

Figure 4: Absolute Change in Percent Predicted FEV_1 from Baseline at Each Visit in Study 445-102 and in Study 445-105 for Patients that Rolled Over from Study 445-102*

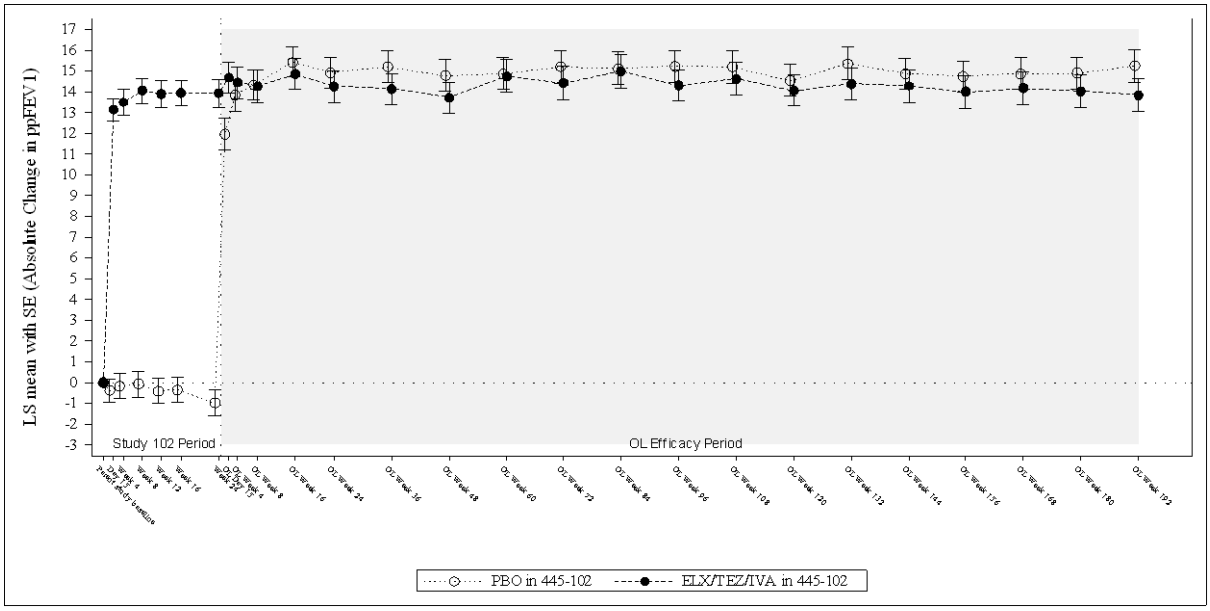


Figure 5: Absolute Change in Percent Predicted FEV_1 from Baseline at Each Visit in Study 445-103 and in Study 445-105 for Patients that Rolled Over from Study 445-103*

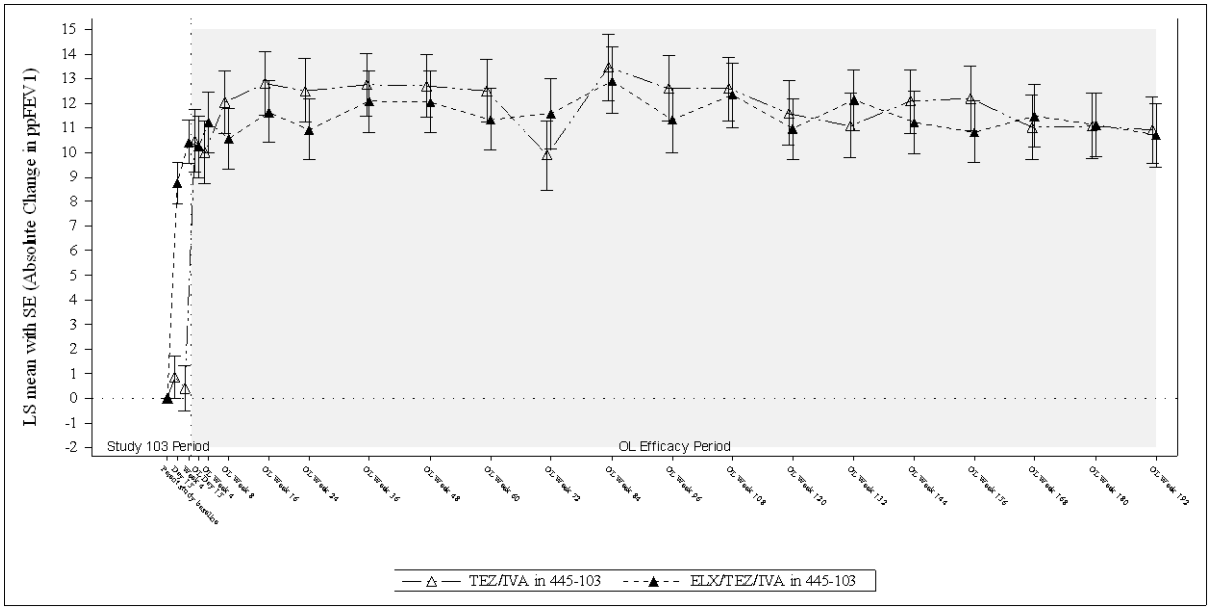


Table 12: Study 445-105 Secondary Efficacy Analysis, Full Analysis Set (F/MF and F/F Subjects)					
Analysis	**Statistic**	**Study 445-105 Week 192**			
		PBO in 445-102 N = 203	**ELX/TEZ/IVA in 445-102 N = 196**	**TEZ/IVA in 445-103 N = 52**	**ELX/TEZ/IVA in 445-103 N = 55**
Absolute change from	n	136	133	32	36
	LS mean	**15.3**	**13.8**	**10.9**	**10.7**

Table 12: Study 445-105 Secondary Efficacy Analysis, Full Analysis Set (F/MF and F/F Subjects)					
Analysis	**Statistic**	**Study 445-105 Week 192**			
		PBO in 445-102 N = 203	**ELX/TEZ/IVA in 445-102 N = 196**	**TEZ/IVA in 445-103 N = 52**	**ELX/TEZ/IVA in 445-103 N = 55**
baseline* in $ppFEV_1$ (percentage points)	95% CI	(13.7, 16.8)	(12.3, 15.4)	(8.2, 13.6)	(8.1, 13.3)
Absolute change from baseline* in SwCl (mmol/L)	n **LS mean** 95% CI	133 **-47.0** (-50.1, -43.9)	128 **-45.3** (-48.5, -42.2)	31 **-48.2** (-55.8, -40.7)	38 **-48.2** (-55.1, -41.3)
Number of PEx during the Cumulative TC Efficacy Period†	Number of events Estimated event rate per year (95% CI)	385 0.21 (0.17, 0.25)		71 0.18 (0.12, 0.25)	
Absolute change from baseline† in BMI (kg/m^2)	n **LS mean** 95% CI	144 **1.81** (1.50, 2.12)	139 **1.74** (1.43, 2.05)	32 **1.72** (1.25, 2.19)	42 **1.85** (1.41, 2.28)
Absolute change from baseline in body weight (kg)	n **LS mean** 95% CI	144 **6.6** (5.5, 7.6)	139 **6.0** (4.9, 7.0)	32 **6.1** (4.6, 7.6)	42 **6.3** (4.9, 7.6)
Absolute change from baseline* in CFQ-R respiratory domain score (points)	n **LS mean** 95% CI	148 **15.3** (12.3, 18.3)	147 **18.3** (15.3,21.3)	33 **14.8** (9.7, 20.0)	42 **17.6** (12.8, 22.4)

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; LS: Least Squares; CI: Confidence Interval; SwCl: Sweat Chloride; PEx: Pulmonary Exacerbations; BMI: Body Mass Index; CFQ-R: Cystic Fibrosis Questionnaire-Revised

* Baseline = parent study baseline

† For subjects who were randomised to the ELX/TEZ/IVA group, the Cumulative TC Efficacy Period includes data from the parent studies through 192 weeks of treatments in Study 445-105 (N=255, including 4 patients that did not rollover into 445-105). For subjects who were randomised to the Placebo or TEZ/IVA group, the Cumulative TC Efficacy Period includes data from 192 weeks of treatments in Study 445-105 only (N=255)

Study 445-106: Study in patients aged 6 to less than 12 years old who are homozygous for the F508del mutation or heterozygous for the F508del mutation and a minimal function mutation.

Study 445-106 was a 24-week open-label study in patients who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation. A

total of 66 patients aged 6 to less than 12 years (mean age at baseline 9.3 years) were dosed according to weight. Patients weighing <30 kg at baseline were administered elexacaftor 100 mg once daily (qd)/tezacaftor 50 mg qd/ivacaftor 75 mg every 12 hours (q12h), and patients weighing ≥ 30 kg at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients had a $ppFEV_1$ ≥ 40% and weighed ≥ 15 kg at screening. The mean $ppFEV_1$ at baseline was 88.8% (range: 39.0%, 127.1%).

The pharmacokinetic profile, safety, and efficacy of TRIKAFTA in patients with CF aged 6 to less than 12 years are supported by evidence from studies of TRIKAFTA in patients aged 12 years and older (Studies 445-102, 445-103, and 445-104), with additional data from a 24-week, open-label, phase 3 study in 66 patients aged 6 to less than 12 years (Study 445-106).

In Study 445-106 the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints were evaluation of pharmacokinetics, and efficacy including absolute change in $ppFEV_1$, sweat chloride (see section 5.1 PHARMACODYNAMIC PROPERTIES), CFQ-R respiratory domain score, and $LCI_{2.5}$ from baseline through Week 24; measure of growth parameters (weight, height, BMI; and associated z-scores) from baseline at Week 24; and number of pulmonary exacerbations from baseline through Week 24. See Table 13 for a summary of secondary efficacy outcomes.

Table 13: Secondary Efficacy Analyses, Full Analysis Set (Study 445-106)

Analysis	Within-Group Change (95% CI) for TRIKAFTA N=66
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	10.2 (7.9, 12.6)
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	-60.9 (-63.7, -58.2)
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	7.0 (4.7, 9.2)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	1.02 (0.76, 1.28)
Absolute change in BMI-for-age z-score from baseline at Week 24	0.37 (0.26, 0.48)
Absolute change in weight from baseline at Week 24 (kg)	3.0 (2.5, 3.5)
Absolute change in weight-for-age z-score from baseline at Week 24	0.25 (0.16, 0.33)
Absolute change in height from baseline at Week 24 (cm)	2.3 (1.9, 2.7)
Absolute change in height-for-age z-score from baseline at Week 24	-0.05 (-0.12, 0.01)
Number of pulmonary exacerbations through Week 24‡	4.0 (0.12) ††
Absolute change in $LCI_{2.5}$ from baseline through Week 24	-1.71 (-2.11, -1.30)

CI: Confidence Interval; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: Body Mass Index; LCI: Lung Clearance Index.
‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.
†† Number of events and estimated event rate per year based on 48 weeks per year.

Study 445-107: An ongoing open label study to evaluate safety and efficacy in patients aged 6 to 11 years who completed Study 445-106.

A 192-week, two-part (part A and part B), open-label extension study to evaluate the safety and efficacy of long-term treatment with ELX/TEZ/IVA is being conducted in patients who

completed Study 445-106. Part A (96 weeks) analysis was conducted in 64 paediatric patients aged 6 years and older and showed sustained improvements in $ppFEV_1$, SwCl, CFQ-R RD score, and $LCI_{2.5}$, consistent with the results observed in the Study 445-106. Secondary efficacy endpoints of the interim analysis are summarised in Table 14.

Table 14: Secondary Efficacy Analysis, Full Analysis Set (N = 64) (Study 445-107 Part A)

Analysis	Statistic	Absolute change from baseline* at week 96
$ppFEV_1$ (percentage points)	n **LS mean** 95% CI	45 **11.2** (8.3, 14.2)
SwCl (mmol/L)	n **LS mean** 95% CI	56 **-62.3** (-65.9, - 58.8)
CFQ-R RD score (points)	n **LS mean** 95% CI	59 **13.3** (11.4, 15.1)
$LCI_{2.5}$	n **LS mean** 95% CI	35 **-2.00** (-2.45, -1.55)
BMI-for-age z-score	n **LS mean** 95% CI	60 **0.24** (0.11, 0.37)
Height-for-age z-score	n **LS mean** 95% CI	60 **0.06** (-0.03, 0.16)
Body weight-for-age z-score	n **LS mean** 95% CI	60 **0.23** (0.10, 0.35)
PEx during the Cumulative Triple Combination (TC) Efficacy Period†	Number of events Observed event rate per year	7 0.04

$ppFEV_1$ = percent predicted Forced Expiratory Volume in 1 second; SwCl = Sweat Chloride; PEx = Pulmonary Exacerbation; BMI = Body Mass Index; CFQ-R RD = Cystic Fibrosis Questionnaire – Revised Respiratory Domain; LS = Least Squares; CI = Confidence Interval; LCI=Lung Clearance Index.

* Baseline = parent study baseline

† The Cumulative TC Efficacy Period includes data from the 66 patients who were enrolled and received at least of one dose of treatment in the parent study (study 445-106 Part B) and/or received at least one dose during study 445-107.

Study 445-111: Study in patients aged 2 to less than 6 years old who had at least one *F508del* mutation or a mutation known to be responsive to TRIKAFTA.

Study 445-111 was a 24-week, open-label study in patients aged 2 to less than 6 years (mean age at baseline 4.1 years). Patients who had at least one *F508del* mutation or a mutation known to be responsive to TRIKAFTA were eligible for the study. A total of 75 patients who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation were enrolled and dosed according to weight. Patients weighing 10 kg to < 14 kg at baseline were administered ELX 80 mg once daily (qd)/TEZ 40 mg qd/IVA 60 mg

once every morning and IVA 59.5 mg once every evening. Patients weighing ≥ 14 kg at baseline were administered ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h.

The pharmacokinetic profile, safety, and efficacy of TRIKAFTA in patients with CF aged 2 to less than 6 years are supported by evidence from studies of TRIKAFTA in patients aged 12 years and older (Studies 445-102, 445-103 and 445-104), with additional data from a 24-week, open-label, phase 3 study in 75 patients aged 2 to less than 6 years (Study 445-111).

In Study 445-111 the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints were an evaluation of pharmacokinetics, and efficacy endpoints of absolute change in sweat chloride (see section 5.1 PHARMACODYNAMIC PROPERTIES) and the mean absolute change in $LCI_{2.5}$ from baseline through Week 24 assessed only on patients aged 3 years and older at screening was 0.83 (95% CI: -1.01, -0.66).

Study 445-124: Study in patients aged 6 years and over with at least one qualifying non-F508del, elexacaftor/tezacaftor/ivacaftor-responsive mutation.
Study 445-124 was a 24 week, randomised, placebo-controlled, double-blind, parallel group study evaluating safety and efficacy of TRIKAFTA in patients with CF aged 6 years and older without an *F508del* mutation. Patients who had at least one qualifying non-*F508del*, elexacaftor/tezacaftor/ivacaftor-responsive mutation (see Table 15) and did not have an exclusionary (other elexacaftor/tezacaftor/ivacaftor -responsive) mutation were eligible for the study. A total of 307 patients were enrolled and dosed according to age and weight. Patients ≥6 to <12 years weighing <30 kg at baseline were administered elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h. Patients ≥6 to <12 years weighing ≥30 kg at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients ≥12 years at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients had a $ppFEV_1$ ≥40% and ≤100% and aged 6 years or older at screening. The mean $ppFEV_1$ at baseline was 67.7% (range: 34.0%, 108.7%)].

Table 15: Eligible ELX/TEZ/IVA-responsive *CFTR* Mutations				
2789+5G>A	*D1152H*	*L997F*	*R1066H*	*T338I*
3272-26A>G	*G85E*	*M1101K*	*R347H*	*V232D*
3849+10kbC>T	*L1077P*	*P5L*	*R347P*	
A455E	*L206W*	*R117C*	*S945L*	

In Study 445-124, the primary endpoint of efficacy was $ppFEV_1$. Secondary endpoints were absolute change in sweat chloride, CFQ-R respiratory domain score, growth parameters (BMI, weight), and number of PEx. See Table 16 for a summary of primary and secondary efficacy outcomes.

Table 16: Primary and Secondary Efficacy Analyses, Full Analysis Set (Study 445-124)			
Analysis	**Statistic**	**Placebo N = 102**	**TRIKAFTA N = 205**
Primary			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.8)	9.2 (7.2, 11.3) *P* < 0.0001 8.9 (0.6)
Secondary			
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.5 (1.6)	-28.3 (-32.1, -24.5) *P* < 0.0001 -27.8 (1.1)

Table 16: Primary and Secondary Efficacy Analyses, Full Analysis Set (Study 445-124)			
Analysis	**Statistic**	**Placebo N = 102**	**TRIKAFTA N = 205**
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.0 (1.6)	19.5 (15.5, 23.5) *P* < 0.0001 17.5 (1.2)
Absolute change from baseline in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.35 (0.09)	0.47 (0.24, 0.69) *P* < 0.0001 0.81 (0.07)
Absolute change from baseline in weight at Week 24 (kg)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.2 (0.3)	1.3 (0.6, 1.9) *P* < 0.0001 2.4 (0.2)
Number of PEx through Week 24	Rate ratio (95% CI) *P* value Number of events Estimated event rate per year	NA NA 40 0.63	0.28 (0.15, 0.51) *P* < 0.0001 21 0.17
BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; IV: intravenous; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor			

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of elexacaftor and tezacaftor and twice-daily dosing of ivacaftor, plasma concentrations of elexacaftor, tezacaftor and ivacaftor reach steady state within approximately 7 days for elexacaftor, within 8 days for tezacaftor, and within 3-5 days for ivacaftor. Upon dosing elexacaftor/tezacaftor/ivacaftor to steady state, the accumulation ratio is approximately 3.6 for elexacaftor, 2.8 for tezacaftor and 4.7 for ivacaftor. Key pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor at steady state in patients with CF aged 12 years and older are shown in Table 17.

Table 17: Mean (SD) Pharmacokinetic Parameters of Elexacaftor, Tezacaftor and Ivacaftor at Steady State in Patients with CF Aged 12 Years and Older			
	Drug	**C_{max} (µg·h/mL)**	**$AUC_{0\text{-}24h,ss}$ or $AUC_{0\text{-}12h,ss}$ (µg·h/mL)***
Elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Elexacaftor	9.15 (2.09)	162 (47.5)
	Tezacaftor	7.67 (1.68)	89.3 (23.2)
	Ivacaftor	1.24 (0.34)	11.7 (4.01)
*$AUC_{0\text{-}24h}$ for elexacaftor and tezacaftor and $AUC_{0\text{-}12h}$ for ivacaftor SD: Standard Deviation; C_{max}: maximum observed concentration; AUC_{ss}: area under the concentration versus time curve at steady state.			

Absorption

The absolute bioavailability of elexacaftor when administered orally in the fed state is approximately 80%. Elexacaftor is absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 6 hours (4 to 12 hours) while the median (range) t_{max} of

tezacaftor and ivacaftor is approximately 3 hours (2 to 4 hours) and 4 hours (3 to 6 hours), respectively.

Elexacaftor exposure (AUC) increases approximately 1.9- to 2.5-fold when administered with a moderate-fat meal relative to fasted conditions. Ivacaftor exposure increases approximately 2.5- to 4.0-fold when administered with fat-containing meals relative to fasted conditions, while food has no effect on the exposure of tezacaftor (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Distribution
Elexacaftor is > 99% bound to plasma proteins and tezacaftor is approximately 99% bound to plasma proteins, in both cases primarily to albumin. Ivacaftor is approximately 99% bound to plasma proteins, primarily to albumin, and also to alpha 1-acid glycoprotein and human gamma-globulin. After oral administration of TRIKAFTA, the mean (±SD) apparent volume of distribution of elexacaftor, tezacaftor and ivacaftor was 53.7 L (17.7), 82.0 L (22.3) and 293 L (89.8), respectively. Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.

Metabolism
Elexacaftor is metabolised extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 200 mg ^{14}C-elexacaftor to healthy male subjects, M23-ELX was the only major circulating metabolite. M23-ELX is considered pharmacologically active.

Tezacaftor is metabolised extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the 3 major circulating metabolites of tezacaftor in humans. M1-TEZ has similar apparent potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active. Another minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of tezacaftor.

Ivacaftor is also metabolised extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolised primarily by CYP3A4/5. M1-IVA and M6-IVA are the two major metabolites of ivacaftor in humans. M1-IVA has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6-IVA is not considered pharmacologically active.

Excretion
Following multiple dosing in the fed state, the mean (±SD) apparent clearance values of elexacaftor, tezacaftor and ivacaftor at steady state were 1.18 (0.29) L/h, 0.79 (0.10) L/h and 10.2 (3.13) L/h, respectively. The mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor following administration of the elexacaftor/tezacaftor/ivacaftor fixed-dose combination tablets are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively. The mean (SD) effective half-lives of elexacaftor, tezacaftor and ivacaftor following administration of the elexacaftor/tezacaftor/ivacaftor fixed-dose combination tablets are approximately 27.4 (9.31) hours, 25.1 (4.93) hours and 15.0 (3.92) hours, respectively.

Following oral administration of ^{14}C-elexacaftor alone, the majority of elexacaftor (87.3%) was eliminated in the faeces, primarily as metabolites.

Following oral administration of ^{14}C-tezacaftor alone, the majority of the dose (72%) was excreted in the faeces (unchanged or as the M2-TEZ) and about 14% was recovered in urine (mostly as M2-TEZ), resulting in a mean overall recovery of 86% up to 26 days after the dose.

Following oral administration of ^{14}C-ivacaftor alone, the majority of ivacaftor (87.8%) was eliminated in the faeces after metabolic conversion.

For elexacaftor, tezacaftor and ivacaftor there was negligible urinary excretion of unchanged drug.

Hepatic impairment
Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of elexacaftor, tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had 25% higher AUC and 12% higher C_{max} for elexacaftor, 73% higher AUC and 70% higher C_{max} for M23-ELX, 36% higher AUC and 24% higher C_{max} for combined ELX and M23-ELX, 20% higher AUC but similar C_{max} for tezacaftor, and 50% higher AUC and 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Tezacaftor and ivacaftor
Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function had an approximately 36% higher AUC and10% higher C_{max} for tezacaftor, and a 1.5-fold higher AUC but similar C_{max} for ivacaftor compared with healthy subjects matched for demographics.

Ivacaftor
In a study with ivacaftor alone, subjects with moderately impaired hepatic function had similar ivacaftor C_{max}, but an approximately 2.0-fold higher ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics.

Renal impairment
Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or in patients with end-stage renal disease.

In human pharmacokinetic studies of elexacaftor, tezacaftor, and ivacaftor, there was minimal elimination of elexacaftor, tezacaftor, and ivacaftor in urine (only 0.23%, 13.7% [0.79% as unchanged drug], and 6.6% of total radioactivity, respectively).

Based on population pharmacokinetic (PK) analysis, exposure of elexacaftor was similar in patients with mild renal impairment (N=75, eGFR 60 to less than 90 mL/min/1.73 m^2) relative to those with normal renal function (N=341, eGFR 90 mL/min/1.73 m^2 or greater).

In population PK analysis conducted in 817 patients administered tezacaftor alone or in combination with ivacaftor in phase 2 or phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Special population

Paediatric patients 2 to less than 18 years of age

Elexacaftor, tezacaftor and ivacaftor exposures observed in phase 3 studies as determined using population PK analysis are presented by age group and dose administered in Table 18. Exposures of elexacaftor, tezacaftor and ivacaftor in patients 2 to less than 18 years of age are within the range observed in patients aged 18 years and older.

Table 18: Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor Exposures Observed at Steady State by Age Group and Dose Administered

Age Group	Dose	ELX $AUC_{0\text{-}24h,ss}$ (µg·h/mL)	TEZ $AUC_{0\text{-}24h,ss}$ (µg·h/mL)	IVA $AUC_{0\text{-}12h,ss}$ (µg·h/mL)
Patients aged 2 to < 6 years weighing < 14 kg (N = 16)	elexacaftor 80 mg qd/ tezacaftor 40 mg qd/ ivacaftor 60 mg qAM and ivacaftor 59.5 mg qPM	128 (24.8)	87.3 (17.3)	11.9 (3.86)
Patients aged 2 to < 6 years weighing ≥ 14 kg (N = 59)	elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h	138 (47.0)	90.2 (27.9)	13.0 (6.11)
Patients aged 6 to <12 years weighing <30 kg (N=36)	elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h	116 (39.4)	67.0 (22.3)	9.78 (4.50)
Patients aged 6 to <12 years weighing≥ 30 kg (N=30)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	195 (59.4)	103 (23.7)	17.5 (4.97)
Adolescent patients (12 to <18 years) (N=72)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	147 (36.8)	88.8 (21.8)	10.6 (3.35)
Adult patients (≥18 years) (N=179)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	168 (49.9)	89.5 (23.7)	12.1 (4.17)

SD: Standard Deviation; AUC_{ss}: area under the concentration versus time curve; qd: once daily; qAM: once every morning; qPM: once every evening; q12h: once every 12 hours.

Gender

Based on population PK analysis, the exposures of elexacaftor, tezacaftor and ivacaftor are similar in males and females.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Elexacaftor, tezacaftor and ivacaftor were all negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay (in TK6 [human lymphoblastoid] cells for elexacaftor, and in Chinese hamster ovary cells for tezacaftor and ivacaftor), and *in vivo* bone marrow micronucleus test (performed in rats with elexacaftor, and in mice for tezacaftor and ivacaftor).

Carcinogenicity
Elexacaftor was not carcinogenic in a 6-month study in transgenic (Tg.rasH2) mice, involving oral administration at doses up to 50 mg/kg/day (yielding systemic exposure 8-fold higher than in patients at the MRHD based on summed AUCs for elexacaftor and M23-ELX). No evidence of tumourigenicity was observed with elexacaftor in rats at oral doses up to 10 mg/kg/day for 92-93 weeks (yielding approximately 2 and 6 times the exposure in patients at the MRHD based on summed AUCs of elexacaftor and its M23 metabolite in male and female rats, respectively).

No evidence of tumourigenicity by tezacaftor was observed in a 6-month study in transgenic (Tg.rasH2) mice and in a conventional 2-year study in rats, conducted by the oral route. The highest doses tested (500 mg/kg/day in mice, 50 mg/kg/day in male rats and 75 mg/kg/day in female rats) yielded exposure to tezacaftor and its M1 and M2 metabolites that was 1.5-fold higher in mice, 1.2-fold higher in male rats, and 2.1-fold higher in female rats than in patients at the MRHD (based on summed AUCs).

Two-year oral studies in mice and rats demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 5- to 9-fold higher than the plasma levels measured in humans following TRIKAFTA therapy, and at least 1.1- to 2.3-fold higher with respect to the summed AUCs for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 20- to 36-fold higher than the plasma levels measured in humans following TRIKAFTA therapy, and 6- to 9-fold higher with respect to the summed AUCs for ivacaftor and its major metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TRIKAFTA film-coated tablets
elexacaftor/tezacaftor/ivacaftor (100 mg/50 mg/75 mg or 50 mg/25 mg/37.5 mg)
Hypromellose
Hypromellose acetate succinate
Sodium lauryl sulfate
Croscarmellose sodium
Microcrystalline cellulose
Magnesium stearate

Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg
OPADRY Complete Film Coating System 20A130036 ORANGE (ARTG PI No: 136412)

Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg
OPADRY Complete Film Coating System 20A130039 ORANGE (ARTG PI No: 141534)

ivacaftor (150 mg or 75 mg)
Silicon dioxide
Croscarmellose sodium
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate
Carnauba wax

Ivacaftor 150 mg
OPADRY II Complete Film Coating System 85F90614 BLUE (ARTG PI No: 108371)
OPACODE monogramming ink S-1-17823 BLACK (ARTG PI No: 12108)

Ivacaftor 75 mg
OPADRY II Complete Film Coating System 85F105098 BLUE (ARTG PI No: 140157)
OPACODE monogramming ink S-1-17823 BLACK (ARTG PI No: 12108)

TRIKAFTA granules
elexacaftor/tezacaftor/ivacaftor (100 mg/50 mg/75 mg or 80 mg/40 mg/60 mg)
Silicon dioxide
Croscarmellose sodium
Hypromellose
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate
Mannitol
Sodium lauryl sulfate
Sucralose

ivacaftor (75 mg or 59.5 mg)
Silicon dioxide
Croscarmellose sodium
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate
Mannitol
Sodium lauryl sulfate
Sucralose

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets
Thermoform blister consisting of PCTFE (polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil lidding.

Pack sizes
TRIKAFTA [co-pack]: Pack size of 84 tablets (56 elexacaftor/tezacaftor/ivacaftor tablets and 28 ivacaftor tablets).

Granules
Biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE) printed foil laminate sachet.

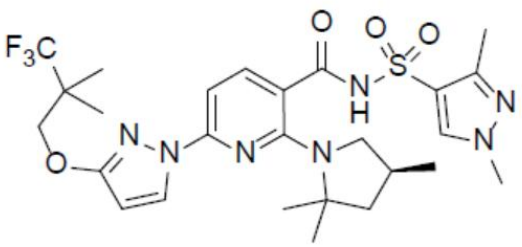
Pack sizes
TRIKAFTA [co-pack]: Pack size of 56 sachets (4 weekly wallets, each with 7 elexacaftor/tezacaftor/ivacaftor sachets and 7 ivacaftor sachets).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

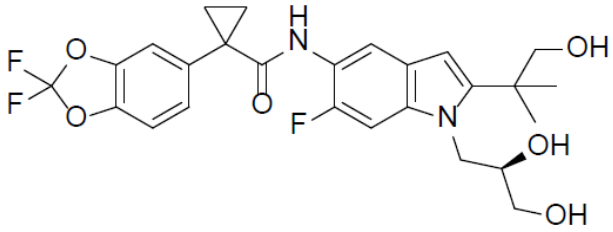
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

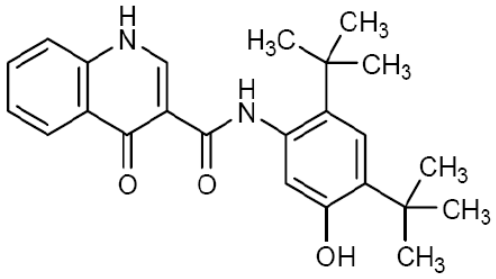
Chemical structure



Elexacaftor: N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide



Tezacaftor: 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide



Ivacaftor: N-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

CAS number
Elexacaftor: 2216712-66-0
Tezacaftor: 1152311-62-0
Ivacaftor: 873054-44-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Vertex Pharmaceuticals (Australia) Pty Ltd
Suite 3, Level 3
601 Pacific Highway
St Leonards,
NSW 2065
Australia
Telephone: 1800 179 987
e-mail: VertexMedicalInfo@vrtx.com

9 DATE OF FIRST APPROVAL

24 March 2021

10 DATE OF REVISION

07 AUG 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE	Updated to include a Warning regarding hypersensitivity reactions, including anaphylaxis.
4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)	Additional descriptive text regarding rash events Table 6: Update to frequency of rash and new footnote to quantify the Rash AE update. Table 7: Update to frequency of rash and new footnote to quantify the Rash AE update. Post Marketing: Addition of Immune system disorders and hypersensitivity
10 DATE OF REVISION	To be updated following approval of this submission.