ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
Kaftrio 75 mg/50 mg/100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets

Each film-coated tablet contains 37.5 mg of ivacaftor, 25 mg of tezacaftor and 50 mg of elexacaftor.

Kaftrio 75 mg/50 mg/100 mg film-coated tablets

Each film-coated tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets

Light orange, capsule-shaped tablet debossed with “T50” on one side and plain on the other (dimensions 6.4 mm × 12.2 mm).

Kaftrio 75 mg/50 mg/100 mg film-coated tablets

Orange, capsule-shaped tablet debossed with “T100” on one side and plain on the other (dimensions 7.9 mm × 15.5 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Kaftrio should only be prescribed by healthcare professionals 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 at least one *CFTR* mutation that is responsive based on clinical and/or *in vitro* data (using a genotype assay) (see section 5.1). Kaftrio should only be used in patients diagnosed with CF. A diagnosis of CF should be made based on diagnostic guidelines and clinical judgement.

There are a limited number of patients who harbour mutations not listed in Table 5 that may be responsive to Kaftrio. In these cases, Kaftrio can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision. This excludes patients with two Class I

(null) mutations (mutations that are known not to produce CFTR protein) as they are not expected to respond to modulator therapy (see sections 4.1, 4.4, and 5.1).

Monitoring of transaminases (ALT and AST) and total bilirubin is recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered (see section 4.4).

Posology

Adults and paediatric patients aged 6 years and older should be dosed according to Table 1.

Table 1: Dosing recommendations for patients aged 6 years and older

Age	Weight	Morning dose	Evening dose
6 to < 12 years	< 30 kg	Two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets	One ivacaftor 75 mg tablet
6 to < 12 years	≥ 30 kg	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet
12 years and older	-	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet

The morning and evening dose should be taken approximately 12 hours apart, with fat-containing food (see Method of administration).

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.
  OR
- 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.

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 2 (see sections 4.4 and 4.5).

Table 2: Dosing schedule for concomitant use with moderate and strong CYP3A inhibitors

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
6 to < 12 years	< 30 kg	Alternate each day: • Two ivacaftor 37.5 mg/ tezacaftor 25 mg/elexacaftor 50 mg tablets on the first day • One ivacaftor 75 mg tablet on the next day No evening ivacaftor tablet dose.	Two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.

6 to < 12 years	≥ 30 kg	Alternate each day: • Two ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg tablets on the first day • One ivacaftor 150 mg tablet on the next day No evening ivacaftor tablet dose.	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.
12 years and older	-	Alternate each day: • Two ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg tablets on the first day • One ivacaftor 150 mg tablet on the next day No evening ivacaftor tablet dose.	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.

Special populations

Elderly
No dose adjustment is recommended for the elderly patient population (see sections 4.4 and 5.2).

Hepatic impairment
Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. For patients with moderate hepatic impairment, the use of Kaftrio should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose (see Table 3).

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 Kaftrio.

No dose adjustment is recommended for patients with mild (Child-Pugh Class A) hepatic impairment (see Table 3) (see sections 4.4, 4.8, and 5.2).

Table 3: Recommendation for use in patients aged 6 years and older with hepatic impairment

Age	Weight	Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
6 to < 12 years	<30 kg	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, Kaftrio should be used with caution at a reduced dose, as follows:	Should not be used

			• Day 1: two ivacaftor 37.5 mg/ tezacaftor 25 mg/elexacaftor 50 mg tablets in the morning • Day 2: one ivacaftor 37.5 mg/ tezacaftor 25 mg/elexacaftor 50 mg tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. The evening dose of the ivacaftor tablet should not be taken.	
6 to < 12 years	≥30 kg	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, Kaftrio should be used with caution at a reduced dose, as follows: • Day 1: two ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg tablets in the morning • Day 2: one ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. The evening dose of the ivacaftor tablet should not be taken.	Should not be used
12 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, Kaftrio should be used with caution at a reduced dose, as follows: • Day 1: two ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg tablets in the morning • Day 2: one ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg tablet in the morning	Should not be used

			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. There is no experience in patients with severe renal impairment or end-stage renal disease (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Kaftrio in combination with ivacaftor (IVA) in children aged less than 2 years have not yet been established. No data are available.

Method of administration

For oral use. Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, crushed, or broken before swallowing because there are no clinical data currently available to support other methods of administration; chewing or crushing the tablet is not recommended.

Kaftrio should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats (see section 5.2).

Food or drink containing grapefruit should be avoided during treatment with Kaftrio (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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. In clinical studies, elevated transaminases were more frequently observed in patients treated with IVA/TEZ/ELX in combination with IVA compared to placebo. In patients taking IVA/TEZ/ELX in combination with IVA, these elevations have sometimes 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 treatment, every 3 months during the first year of treatment and annually thereafter (see section 4.2).

For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt treatment and promptly measure serum transaminases and total bilirubin if a patient develops clinical signs or symptoms of liver injury. Interrupt dosing in the event of ALT or AST >5 × the upper limit of normal (ULN), or ALT or AST >3 × ULN with total bilirubin >2 × ULN. Closely monitor the

laboratory tests until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment. Patients who resume treatment after interruption should be monitored closely.

In patients with pre-existing advanced liver disease, IVA/TEZ/ELX in combination with IVA should be used with caution and only if the benefits are expected to outweigh the risks (see sections 4.2, 4.8, and 5.2).

Hepatic impairment

Treatment of patients with moderate hepatic impairment is not recommended. For patients with moderate hepatic impairment, the use of IVA/TEZ/ELX should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose (see Table 3).

Patients with severe hepatic impairment should not be treated with IVA/TEZ/ELX (see sections 4.2, 4.8, and 5.2).

Depression

Depression (including suicidal ideation and suicide attempt) has been reported in patients treated with IVA/TEZ/ELX, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders (see section 4.8). In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, unusual changes in behaviour, anxiety, or insomnia and to seek medical advice immediately if these symptoms present.

Paediatric population
In young children (aged 2-5 years) treated with IVA/TEZ/ELX behavioural changes have been reported, which occurred usually within the first two months of treatment initiation. In some cases, symptom improvement was reported after treatment discontinuation.

Renal impairment

There is no experience in patients with severe renal impairment/end-stage renal disease therefore caution is recommended in this population (see sections 4.2 and 5.2).

Mutations unlikely to respond to modulator therapy

Patients with a genotype consisting of two *CFTR* mutations that are known not to produce CFTR protein (i.e., two Class I mutations) are not expected to respond to Kaftrio treatment.

Clinical studies comparing IVA/TEZ/ELX to TEZ/IVA or IVA

No clinical study has been conducted to directly compare IVA/TEZ/ELX to TEZ/IVA or IVA in patients not harbouring *F508del* variants.

Patients after organ transplantation

IVA/TEZ/ELX in combination with IVA 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 for interactions with commonly used immunosuppressants.

Rash events

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 IVA/TEZ/ELX was continued and the rash resolved without treatment. Children have a higher incidence rate compared to adults. The incidence of rash events was also higher in females compared to males, particularly in females taking hormonal contraceptives (see section 4.8). A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, interrupting treatment with IVA/TEZ/ELX in combination with IVA and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming IVA/TEZ/ELX in combination with IVA without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered (see section 4.8).

Elderly

Clinical studies of IVA/TEZ/ELX in combination with IVA did not include sufficient number of patients aged 65 years and older to determine whether response in these patients is different from younger adults. Dose recommendations are based on the pharmacokinetic profile and knowledge from studies with tezacaftor/ivacaftor (TEZ/IVA) in combination with IVA, and IVA monotherapy (see sections 4.2 and 5.2).

Interactions with medicinal products

CYP3A inducers
Exposure to IVA is significantly decreased and exposures to ELX and TEZ are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduced efficacy of IVA/TEZ/ELX and IVA; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors
Exposures of ELX, TEZ and IVA are increased when co-administered with strong or moderate CYP3A inhibitors. The dose of IVA/TEZ/ELX and IVA should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see section 4.5 and Table 2 in section 4.2).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with IVA-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 IVA cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with IVA/TEZ/ELX in combination with IVA (see section 5.3).

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products affecting the pharmacokinetics of ELX, TEZ and/or IVA

CYP3A inducers

ELX, TEZ and IVA are substrates of CYP3A (IVA is a sensitive substrate of CYP3A). Concomitant use of strong CYP3A inducers may result in reduced exposures and thus reduced IVA/TEZ/ELX efficacy. Co-administration of IVA with rifampicin, a strong CYP3A inducer, significantly decreased IVA area under the curve (AUC) by 89%. ELX and TEZ exposures are also expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.4).

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 ELX AUC by 2.8-fold and TEZ AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, IVA AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of IVA/TEZ/ELX and IVA should be reduced when co-administered with strong CYP3A inhibitors (see Table 2 in section 4.2 and section 4.4).

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

Simulations indicated that co-administration with moderate CYP3A inhibitors fluconazole, erythromycin and verapamil, may increase ELX and TEZ AUC by approximately 1.9- to 2.3-fold. Co-administration of fluconazole increased IVA AUC by 2.9-fold. The dose of IVA/TEZ/ELX and IVA should be reduced when co-administered with moderate CYP3A inhibitors (see Table 2 in section 4.2 and section 4.4).

Examples of moderate CYP3A inhibitors include:
- fluconazole
- erythromycin

Co-administration with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ELX, TEZ and IVA. Food or drink containing grapefruit should be avoided during treatment with IVA/TEZ/ELX and IVA (see section 4.2).

Ciprofloxacin
ELX/TEZ/IVA was not evaluated for concomitant use with ciprofloxacin. However, ciprofloxacin had no clinically relevant effect on the exposure of TEZ or IVA and is not expected to have a clinically relevant effect on the exposure of ELX. Therefore, no dose adjustment is necessary during concomitant administration of IVA/TEZ/ELX with ciprofloxacin.

Potential for interaction with transporters
In vitro studies showed that ELX is a substrate for the efflux transporters P-gp and Breast Cancer Resistance Protein (BCRP) but is not a substrate for OATP1B1 or OATP1B3. Exposure to ELX is not expected to be affected significantly by concomitant use of P-gp and BCRP inhibitors due to its high intrinsic permeability and low likelihood of being excreted intact.

In vitro studies showed that TEZ is a substrate for the uptake transporter OATP1B1 and efflux transporters P-gp and BCRP. TEZ is not a substrate for OATP1B3. Exposure to TEZ is not expected to be affected significantly by concomitant inhibitors of OATP1B1, P-gp, or BCRP due to its high intrinsic permeability and low likelihood of being excreted intact. However, exposure to M2-TEZ (TEZ metabolite) may be increased by inhibitors of P-gp. Therefore, caution should be used when P-gp inhibitors (e.g., ciclosporin) are used with IVA/TEZ/ELX.

In vitro studies showed that IVA is not a substrate for OATP1B1, OATP1B3, or P-gp. IVA and its metabolites are substrates of BCRP *in vitro*. Due to its high intrinsic permeability and low likelihood of being excreted intact, co-administration of BCRP inhibitors is not expected to alter exposure of IVA and M1-IVA, while any potential changes in M6-IVA exposures are not expected to be clinically relevant.

Medicinal products affected by ELX, TEZ and/or IVA

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

Potential for interaction with transporters
Co-administration of IVA or TEZ/IVA with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by IVA. Administration of IVA/TEZ/ELX and IVA 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.

ELX and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. TEZ/IVA increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration with IVA/TEZ/ELX in combination with IVA 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 ELX and M23-ELX.

ELX and IVA are inhibitors of BCRP. Co-administration of IVA/TEZ/ELX, and IVA may increase exposures of medicinal products that are substrates of BCRP, such as rosuvastatin. When used concomitantly with substrates of BCRP, appropriate monitoring should be used.

Hormonal contraceptives

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of ELX, TEZ, or IVA in pregnant women. Animal studies do not

indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of IVA/TEZ/ELX during pregnancy.

Breast-feeding

Limited data show that ELX, TEZ, and IVA are excreted in human milk and have been quantified in plasma of breastfed newborns/infants of treated women. There is insufficient information on the effects of IVA/TEZ/ELX in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from IVA/TEZ/ELX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of ELX, TEZ and IVA on fertility in humans. TEZ had no effects on fertility and reproductive performance indices in male and female rats at clinically relevant exposures. ELX and IVA had an effect on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

IVA/TEZ/ELX in combination with IVA has a minor influence on the ability to drive or use machines. Dizziness has been reported in patients receiving IVA/TEZ/ELX in combination with IVA, TEZ/IVA in combination with IVA as well as IVA (see section 4.8). Patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions experienced by patients aged 12 years and older who received IVA/TEZ/ELX in combination with IVA were headache (17.3%), diarrhoea (12.9%), upper respiratory tract infection (11.9%) and aminotransferase increased (10.9%).

Serious adverse reactions of rash experienced by patients aged 12 years and older were reported in 1.5% patients treated with IVA/TEZ/ELX in combination with IVA (see section 4.4).

Tabulated list of adverse reactions

Table 4 reflects adverse reactions observed with IVA/TEZ/ELX in combination with IVA, TEZ/IVA in combination with IVA, and IVA monotherapy. Adverse reactions are listed by MedDRA system organ class and frequency: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions		
MedDRA System Organ Class	**Adverse Reactions**	**Frequency**
Infections and infestations	Upper respiratory tract infection*, Nasopharyngitis	very common
	Rhinitis*, Influenza*	common
Immune system disorders	Hypersensitivity	not known
Metabolism and nutrition disorders	Hypoglycaemia*	common
Psychiatric disorders	Depression, Behavioural changes	not known
Nervous system disorders	Headache*, Dizziness*	very common
Ear and labyrinth disorders	Ear pain, Ear discomfort, Tinnitus, Tympanic membrane hyperaemia, Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain, Nasal congestion*	very common
	Rhinorrhoea*, Sinus congestion, Pharyngeal erythema, Abnormal breathing*	common
	Wheezing*	uncommon
Gastrointestinal disorders	Diarrhoea*, Abdominal pain*	very common
	Nausea, Abdominal pain upper*, Flatulence*	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*	very common
	Aspartate aminotransferase increased*	very common
	Liver injury†, Total bilirubin increase†	not known
Skin and subcutaneous tissue disorders	Rash*	very common
	Acne*, Pruritus*	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation, Gynaecomastia, Nipple disorder, Nipple pain	uncommon
Investigations	Bacteria in sputum, Blood creatine phosphokinase increased*	very common
	Blood pressure increased*	uncommon
*Adverse reactions observed during clinical studies with IVA/TEZ/ELX in combination with IVA. † Liver injury (ALT and AST and total bilirubin increase) reported from post-marketing data with IVA/TEZ/ELX in combination with IVA. Frequency cannot be estimated from the available data.		

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 aged 12 years and older (study 445-103).
- A 192-week, open-label safety and efficacy study (study 445-105) in 506 patients who rolled over from studies 445-102 and 445-103.
- An 8-week, randomised, double-blind, active-controlled study in 258 patients aged 12 years and older (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, randomised, placebo-controlled study (study 445-116) in 121 patients aged 6 to less than 12 years.

- A 192-week, two-part (part A and part B), open-label safety and efficacy study (study 445-107) in 64 patients aged 6 years and older who rolled over from study 445-106.
- A 24-week, open-label study (study 445-111) in 75 patients aged 2 to less than 6 years.
- A 24-week, randomised, double-blind, placebo-controlled study (study 445-124) in 307 patients aged 6 years and older.

Description of selected adverse reactions

Transaminase elevations
In study 445-102, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 × the ULN was 1.5%, 2.5% and 7.9% in IVA/TEZ/ELX-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 IVA/TEZ/ELX-treated patients and 4.0% in placebo-treated patients.

During the open-label studies, some patients discontinued treatment due to elevated transaminases. Post-marketing cases of treatment discontinuation due to elevated transaminases have been reported (see section 4.4).

Rash events
Studies in IVA/TEZ/ELX-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 IVA/TEZ/ELX-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients. In patients treated with IVA/TEZ/ELX, 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).

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 IVA/TEZ/ELX was continued and the rash resolved without treatment.

Increased creatine phosphokinase
In study 445-102, the incidence of maximum creatine phosphokinase >5 × the ULN was 10.4% in IVA/TEZ/ELX- and 5.0% in placebo-treated patients. The observed creatine phosphokinase elevations were generally transient and asymptomatic and many were preceded by exercise.

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 IVA/TEZ/ELX-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%, respectively in IVA/TEZ/ELX-treated patients compared with 3.5% and 3.5%, respectively in placebo-treated patients.

Paediatric population

The safety data of IVA/TEZ/ELX in combination with IVA in studies 445-102, 445-103, 445-104, 445-106, 445-111, and 445-124 and was evaluated in 272 patients between 2 to less than 18 years of age. The safety profile is generally consistent among paediatric and adult patients.

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 × ULN were 0.0%, 1.5%, and 10.6%, respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

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 × ULN were 1.3%, 2.7%, and 8.0% respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

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.

Lenticular opacity
One patient had an adverse event of lenticular opacity.

Behavioural changes
Most cases of behavioural changes have been reported in younger children aged 2-5 years.

Other special populations

With the exception of sex differences in rash, the safety profile of IVA/TEZ/ELX in combination with IVA was generally similar across all subgroups of patients, including analysis by age, baseline percent predicted forced expiratory volume in one second ($ppFEV_1$) and geographic regions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

ELX and TEZ 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 CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of ELX, TEZ and IVA is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

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

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

In CF, the presence of one *CFTR* mutation responsive to IVA/TEZ/ELX based on *in vitro* data in FRT cells, will likely result in a clinical response.

Table 5 lists *CFTR* mutations included in the indication for treatment with Kaftrio. The occurrence of *CFTR* mutations listed in this table should not be used in lieu of a diagnosis of cystic fibrosis, nor as a sole determinant for prescribing purposes.

Table 5: *CFTR* mutations identified to be responsive to IVA/TEZ/ELX based on clinical and/or *in vitro* data

293A→G	E264V	H939R	N1088D	S108F
314del9	E282D	H939R;H949L[‡]	N1195T	S158N
546insCTA	E292K	H954P	N1303I	S182R
548insTAC	E384K	H1054D	N1303K[*]	S308P
711+3A→G[*]	E403D	H1079P	P5L[†]	S341P
1140-1151dup	E474K	H1085P	P67L[*]	S364P
1461insGAT	E527G	H1085R	P111L	S434P
1507_1515del9	E588V	H1375N	P140S	S492F
2055del9	E822K	H1375P	P205S	S519G
2183A→G	E831X	I86M	P439S	S531P
2789+5G→A[*]	E1104K	I105N	P499A	S549I
2851A/G	E1104V	I125T	P574H	S549N
3007del6	E1126K	I148L	P750L	S549R[*]
3132T→G	E1221V	I148N	P798S	S557F
3141del9	E1228K	I175V	P988R	S589I
3143del9	E1409K	I331N	P1013H	S589N
3272-26A→G[*†]	E1433K	I336K	P1013L	S624R
3331del6	F87L	I336L	P1021L	S686Y
3410T→C	F191V	I444S	P1021T	S737F
3523A→G	F200I	I497S	P1372T	S821G
3601A→C	F311del	I502T	Q30P	S898R
3761T→G	F311L	I506L	Q98P	S912L

3791C/T	F312del	I506V	Q98R	S912L;G1244V‡
3849+10kbC→T*†	F433L	I506V;D1168G‡	Q151K	S912T
3850G→A	F508C;S1251 N‡	I521S	Q179K	S945L*†
3978G→C	F508del*	I530N	Q237E	S955P
A46D	F508del;R1438W‡	I556V	Q237H	S977F
A62P	F575Y	I586V	Q237P	S977F;R1438W‡
A107G	F587I	I601F	Q359K;T360K‡	S1045Y
A120T	F587L	I618N	Q359R	S1118F
A141D	F693L(TTG)	I618T	Q372H	S1159F
A155P	F932S	I980K	Q493L	S1159P
A234D	F1016S	I1023R	Q493R	S1188L
A234V	F1052V	I1139V	Q552P	S1251N
A238V	F1074L	I1203V	Q1012P	S1255P
A309D	F1078S	I1234L	Q1209P	T338I
A349V	F1099L	I1234V	Q1291H	T351I
A357T	F1107L	I1269N	Q1291R	T351S
A455E*†	G27E	I1366N	Q1313K	T351S;R851L‡
A455V	G27R	I1366T	Q1352H	T388M
A457T	G126D	K162E	R31L	T465I
A462P	G178E	K464E	R74Q	T501A
A534E	G178R	K464N	R74Q;R297Q‡	T582S
A554E	G194R	K522E	R74Q;V201M;D1270N‡	T908N
A566D	G194V	K522Q	R74W	T990I
A872E	G213E	K951E	R74W;D1270N‡	T1036N*
A1006E	G213E;R668C‡	K1060T	R74W;R1070W;D1270N‡	T1057R
A1025D	G213V	L15P	R74W;S945L‡	T1086A
A1067P	G226R	L15P;L1253F‡	R74W;V201M‡	T1086I
A1067T	G239R	L32P	R74W;V201M;D1270N‡	T1246I
A1067V	G253R	L88S	R74W;V201M;L997F‡	T1299I
A1081V	G314E	L102R;F1016S‡	R75L	T1299K
A1087P	G314R	L137P	R75Q;L1065P‡	V11I
A1319E	G424S	L159S	R75Q;N1088D‡	V93D
A1374D	G437D	L165S	R75Q;S549N‡	V201M
A1466S	G461R	L167R	R117C†	V232A
C225R	G461V	L206W*†	R117C;G576A;R668C‡	V232D
C491R	G463V	L210P	R117G	V317A
C590Y	G480C	L293P	R117H*	V322M
C866Y	G480D	L327P	R117L	V392G
c.1367_1369dupTTG	G480S	L333F	R117L;L997F‡	V456A
D58H	G500D	L333H	R117P	V456F
D58V	G545R	L346P	R248K	V520I
D110E	G551A	L441P	R258G	V562I;A1006E‡
D110H	G551D*	L453S	R297Q	V562L
D110N	G551R	L467F	R334L	V591A
D192G	G551S	L558F	R334Q	V603F
D192N	G576A;R668C‡	L619S	R334W†	V920L
D373N	G576A;S1359Y‡	L633P	R347H*	V920M
D426N	G622D	L636P	R347L	V1008D
D443Y	G622V	L927P	R347P	V1010D
D443Y;G576A;R668C‡	G628A	L967F;L1096R‡	R352Q	V1153E
D529G	G628R	L973F	R352W	V1240G
D565G	G85E*†	L1011S	R516S	V1293G

D567N	G930E	L1065R	R553Q	V1293I
D579G	G970D	L1077P*†	R555G	V1415F
D614G	G970S	L1227S	R600S	W202C
D651H	G970V	L1324P	R709Q	W361R
D651N	G1047D	L1335P	R751L	W496R
D806G	G1047R	L1388P	R792G	W1098C
D924N	G1061R	L1480P	R792Q	W1282G
D979A	G1069R	M150K	R810G	W1282R
D979V	G1123R	M150R	R851L	Y89C
D985H	G1173S	M152L	R933G	Y109H
D985Y	G1237V	M152V	R1048G	Y109N
D993A	G1244E	M265R	R1066C†	Y122C
D993G	G1244R	M348K	R1066G	Y161C
D993Y	G1247R	M394L	R1066H*†	Y161D
D1152A	G1249E	M469V	R1070P	Y161S
D1152H*†	G1249R	M498I	R1070Q	Y301C
D1270N*	G1265V	M952I	R1070W	Y563N
D1270Y	G1298V	M952T	R1162Q	Y913S
D1312G	G1349D	M961L	R1239S	Y919C
D1377H	G149R;G576A;R668C‡	M1101K*†	R1283G	Y1014C
D1445N	H139L	M1137R	R1283M	Y1032C
E56K	H139R	M1137V	R1283S	Y1032N
E60K	H146R	M1210K	R1438W	Y1073C
E92K	H199Q	N186K	S13F	Y1092H
E116K	H199Y	N187K	S13P	Y1381H
E116Q	H609L	N396Y	S18I	
E193K	H620P	N418S	S18N	
E217G	H620Q	N900K	S50P	

There are people with CF harbouring two rare, non-*F508del CFTR* mutations not listed in Table 5. Provided that they do not harbour two Class I (null) mutations (mutations that are known not to produce CFTR protein) (see section 4.1), they may respond to treatment. In these cases, Kaftrio can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision.

The individual diagnosis of CF should be based on diagnostic guidelines and clinical judgement as considerable variability exists in phenotype for patients harbouring the same genotype.

* Mutations supported by clinical data.
† Mutations supported by Real-World data in ≥ 5 patients.
‡ Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
Non-annotated mutations are included based on the FRT assay in which a positive response is indicative of a clinical response.

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 predicts either no production of a CFTR protein or a CFTR protein that does not transport chloride and is not responsive to other CFTR modulators [IVA and TEZ/IVA] *in vitro*), a reduction in sweat chloride was observed from baseline at week 4 and sustained through the 24-week treatment period. The treatment difference of IVA/TEZ/ELX in combination with IVA 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 IVA/TEZ/ELX in combination with IVA compared to TEZ/IVA in combination with IVA 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 mutation on the second allele with a gating defect or residual CFTR activity), the mean absolute change in sweat chloride from baseline through week 8 for the IVA/TEZ/ELX in combination with IVA group was -22.3 mmol/L (95% CI: -24.5, -20.2; $P < 0.0001$). The treatment difference of IVA/TEZ/ELX in combination with IVA compared to the control group (IVA group or TEZ/IVA in combination with IVA group) 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 (n=62) through week 24 (n=60) was -60.9 mmol/L (95% CI: -63.7, -58.2)[*]. The mean absolute change in sweat chloride from baseline through week 12 (n=59) was -58.6 mmol/L (95% CI: -61.1, -56.1).

[*] Not all participants included in the analyses had data available for all follow-up visits, especially from week 16 onwards. The ability to collect data at week 24 was hampered by the COVID-19 pandemic. Week 12 data were less impacted by the pandemic.

In study 445-116 (patients aged 6 to less than 12 years who are heterozygous for the *F508del* mutation and a minimal function mutation), treatment with IVA/TEZ/ELX in combination with IVA resulted in reduction in sweat chloride through week 24, as compared to placebo. The LS mean treatment difference for the IVA/TEZ/ELX in combination with IVA group versus placebo for absolute change in sweat chloride from baseline through week 24 was -51.2 mmol/L (95% CI: -55.3, -47.1; nominal $P < 0.0001$).

In study 445-124 (patients aged 6 years and older with a qualifying non-*F508del*, IVA/TEZ/ELX-responsive *CFTR* mutation [see Table 6]), 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 ELX and 3 times the maximum recommended dose of TEZ and IVA, 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 IVA/TEZ/ELX-treated patients.

Clinical efficacy and safety

The efficacy of IVA/TEZ/ELX in combination with IVA in patients with CF was demonstrated in six phase 3 studies. Patients enrolled in these studies were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a mutation with minimal function (MF), a gating defect, or residual CFTR activity on the second allele. Study 445-124 enrolled patients who had at least one qualifying non-*F508del,* IVA/TEZ/ELX-responsive *CFTR* mutation (see Table 6).

Study 445-102 was a 24-week, randomised, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and an MF mutation on the second allele. CF patients eligible for this study were required to either have Class I mutations that predicted no CFTR protein being produced (including nonsense mutations, canonical splice mutations and insertion/deletion frameshift mutations both small (≤3 nucleotide) and non-small (>3 nucleotide)), or missense mutations which results in CFTR protein that does not transport chloride and is not responsive to IVA and TEZ/IVA *in vitro*. The most frequent alleles with minimal function assessed in the study were *G542X*, *W1282X*, *R553X*, and *R1162X*; *621+1G→T*, *1717-1G→A*, and *1898+1G→A*; *3659delC*, and *394delTT*; *CFTRdele2,3*; and *N1303K*, *I507del*, *G85E*, *R347P*, and *R560T*. A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomised and dosed to receive placebo or IVA/TEZ/ELX in combination with IVA. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%).

Study 445-103 was a 4-week, randomised, double-blind, active-controlled study in patients who were homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received TEZ/IVA in combination with IVA during a 4-week open-label run-in period and were then randomised and dosed to receive either IVA/TEZ/ELX in combination with IVA or TEZ/IVA in combination with IVA 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 run-in period was 60.9% (range: 35.0%, 89.0%).

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

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 two IVA 37.5 mg/TEZ 25 mg/ELX 50 mg tablets in the morning and one IVA 75 mg tablet in the evening. Patients weighing ≥30 kg at baseline were administered two IVA 75 mg/TEZ 50 mg/ELX 100 mg tablets in the morning and one IVA 150 mg tablet in the evening. 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%).

Study 445-116 was a 24-week, randomised, double-blind, placebo-controlled study in patients aged 6 to less than 12 years (mean age at baseline 9.2 years) who were heterozygous for the *F508del* mutation and a minimal function mutation. A total of 121 patients were randomised to receive either placebo or IVA/TEZ/ELX in combination with IVA. Patients who received IVA/TEZ/ELX in combination with IVA weighing <30 kg at baseline were administered two IVA 37.5 mg/TEZ 25 mg/ELX 50 mg tablets in the morning and one IVA 75 mg tablet in the evening. Patients weighing ≥30 kg at baseline were administered two IVA 75 mg/TEZ 50 mg/ELX 100 mg tablets in the morning and one IVA 150 mg tablet in the evening. At screening, patients had a $ppFEV_1$ ≥70% [mean $ppFEV_1$ at baseline of 89.3% (range: 44.6%, 121.8%)], $LCI_{2.5}$ result ≥7.5 [mean $LCI_{2.5}$ at baseline of 10.01 (range: 6.91, 18.36)], and weighed ≥15 kg.

Study 445-124 was a 24-week, randomised, placebo-controlled, double-blind, parallel group study in patients aged 6 years and older. Patients who had at least one qualifying non-*F508del*, IVA/TEZ/ELX-responsive *CFTR* mutation (see Table 6) and did not have an exclusionary (other IVA/TEZ/ELX-responsive) mutation were eligible for the study.

Table 6: Eligible IVA/TEZ/ELX-responsive *CFTR* mutations				
2789+5G>A	*D1152H*	*L997F*	*R117C*	*T338I*
3272-26A>G	*G85E*	*M1101K*	*R347H*	*V232D*
3849+10kbC>T	*L1077P*	*P5L*	*R347P*	
A455E	*L206W*	*R1066H*	*S945L*	

A total of 307 patients were enrolled and dosed according to age and weight. Patients ≥6 to <12 years weighing <30 kg at baseline (n=31) were administered ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. Patients ≥6 to <12 years weighing ≥30 kg at baseline were administered ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Patients ≥12 years at baseline were administered ELX 200 mg qd/TEZ 100 mg qd/IVA 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%).

Patients in these studies 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 medicinal products. Patients had a confirmed diagnosis of CF.

Study CFD-016 was an observational, retrospective study evaluating Real-World clinical outcomes in patients aged 6 years and older. Patients had at least one IVA/TEZ/ELX-responsive mutation and did not have an *F508del* mutation. A total of 422 patients were evaluated with a total of 82 IVA/TEZ/ELX-responsive non-*F508del* mutations represented. The mean $ppFEV_1$ at baseline was 74.15%.

In studies 445-102, 445-103, 445-104, 445-106, and 445-124 patients 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 × ULN, or total bilirubin ≥2 × ULN), were 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, 445-116, and 445-124 were eligible to roll over into separate open-label extension studies.

Study 445-102
In study 445-102 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through week 24. Treatment with IVA/TEZ/ELX in combination with IVA 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 7). Mean improvement in $ppFEV_1$ was observed at the first assessment on day 15 and sustained through the 24-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region.

A total of 18 patients receiving IVA/TEZ/ELX in combination with IVA had $ppFEV_1$ <40 percentage points at baseline. The safety and efficacy in this subgroup were consistent to those observed in the overall population. The mean treatment difference of IVA/TEZ/ELX in combination with IVA- compared to placebo-treated patients for absolute change in $ppFEV_1$ through week 24 in this subgroup was 18.4 percentage points (95% CI: 11.5, 25.3).

See Table 7 for a summary of primary and key secondary outcomes.

Table 7: Primary and key secondary efficacy analyses, full analysis set (study 445-102)			
Analysis	**Statistic**	**Placebo N=203**	**IVA/TEZ/ELX in combination with IVA N=200**
Primary			
Baseline $ppFEV_1$	Mean (SD)	61.3 (15.5)	61.6 (15.0)
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
Baseline sweat chloride (mmol/L)	Mean (SD)	102.9 (9.8)	102.3 (11.9)
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 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)
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	70.0 (17.8)	68.3 (16.9)
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 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)
Baseline BMI (kg/m^2)	Mean (SD)	21.31 (3.14)	21.49 (3.07)
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)

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SD: Standard Deviation; 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.

Study 445-103

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 IVA/TEZ/ELX in combination with IVA compared to TEZ/IVA in combination with IVA 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 8). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region.

See Table 8 for a summary of primary and key secondary outcomes in the overall trial population.

In a post-hoc analysis of patients with (N=66) and without (N=41) recent CFTR modulator use, an improvement in $ppFEV_1$ of 7.8 percentage points (95% CI: 4.8, 10.8) and 13.2 percentage points (95% CI: 8.5, 17.9), respectively was observed.

Table 8: Primary and key secondary efficacy analyses, full analysis set (study 445-103)

Analysis*	Statistic	TEZ/IVA in combination with IVA N=52	IVA/TEZ/ELX in combination with IVA N=55
Primary			
Baseline $ppFEV_1$	Mean (SD)	60.2 (14.4)	61.6 (15.4)
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			
Baseline sweat chloride (mmol/L)	Mean (SD)	90.0 (12.3)	91.4 (11.0)
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)
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	72.6 (17.9)	70.6 (16.2)
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; SD: Standard Deviation; 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 TEZ/IVA in combination with IVA.

Study 445-104

In study 445-104 the primary endpoint was within-group mean absolute change in $ppFEV_1$ from baseline through week 8 for the IVA/TEZ/ELX in combination with IVA group. Treatment with IVA/TEZ/ELX in combination with IVA resulted in statistically significant improvement in $ppFEV_1$ from baseline of 3.7 percentage points (95% CI: 2.8, 4.6; $P < 0.0001$) (see Table 9). Overall improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, geographic region, and genotype groups (F/Gating or F/RF).

See Table 9 for a summary of primary and secondary outcomes in the overall trial population.

In a subgroup analysis of patients with an F/Gating genotype, the treatment difference of IVA/TEZ/ELX in combination with IVA (N=50) compared with IVA (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 IVA/TEZ/ELX in combination with IVA (N=82) compared with TEZ/IVA in

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

Table 9: Primary and secondary efficacy analyses, full analysis set (study 445-104)

Analysis*	Statistic	Control group† N=126	IVA/TEZ/ELX in combination with IVA N=132
Primary			
Baseline $ppFEV_1$	Mean (SD)	68.1 (16.4)	67.1 (15.7)
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 $ppFEV_1$ 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) $P < 0.0001$
Baseline sweat chloride (mmol/L)	Mean (SD)	56.4 (25.5)	59.5 (27.0)
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 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) $P < 0.0001$
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	77.3 (15.8)	76.5 (16.6)
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 (points) compared to the control group	Treatment difference (95% CI)	NA	8.7 (5.3, 12.1)

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SD: Standard Deviation; 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 IVA or TEZ/IVA in combination with IVA.
† IVA group or TEZ/IVA in combination with IVA group.

Study 445-105
Study 445-105 was a 192-week open-label extension study to evaluate the safety and efficacy of long-term treatment with IVA/TEZ/ELX in combination with IVA. Patients who rolled over from studies 445-102 (N=399) and 445-103 (N=107) received IVA/TEZ/ELX in combination with IVA.

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 IVA/TEZ/ELX in combination with IVA in the parent studies. Patients from the control arms as well as patients who received IVA/TEZ/ELX in combination with IVA in the parent studies, showed sustained improvements. Secondary efficacy endpoints are summarised in Table 10.

Table 10: Study 445-105 secondary efficacy analysis, full analysis set (F/MF and F/F subjects)					
Analysis	**Statistic**	**Study 445-105 week 192**			
		Placebo in 445-102 N=203	**IVA/TEZ/ELX in 445-102 N=196**	**TEZ/IVA in 445-103 N=52**	**IVA/TEZ/ELX in 445-103 N=55**
Absolute change from baseline* in $ppFEV_1$ (percentage points)	n **LS mean** 95% CI	136 **15.3** (13.7, 16.8)	133 **13.8** (12.3, 15.4)	32 **10.9** (8.2, 13.6)	36 **10.7** (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 Triple Combination (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 RD 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; 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; n = size of subsample

* Baseline = parent study baseline.

† For subjects who were randomised to the IVA/TEZ/ELX 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 study 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 445-124

The safety and efficacy of IVA/TEZ/ELX in 307 patients with CF aged 6 years and older without an *F508del* mutation but with a qualifying IVA/TEZ/ELX-responsive *CFTR* mutation were evaluated (study 445-124).

In study 445-124 the primary endpoint of efficacy was mean absolute change in $ppFEV_1$ from baseline through week 24. Secondary endpoints were absolute change in sweat chloride, CFQ-R respiratory domain score, growth parameters (BMI, weight), and number of PEx. See Table 11 for a summary of primary and secondary efficacy outcomes.

Table 11: Primary and secondary efficacy analyses, full analysis set (study 445-124)			
Analysis	**Statistic**	**Placebo N=102**	**IVA/TEZ/ELX 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)
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; CI: Confidence Interval; IV: intravenous; IVA: ivacaftor; LS: Least Squares; N: total sample size; *P*: probability; PEx: Pulmonary Exacerbation; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; SE: Standard Error; SwCl: Sweat Chloride; TEZ: tezacaftor			

Study CFD-016
Study CFD-016 included 422 homozygotic non-*F508del* CF patients harbouring at least one IVA/TEZ/ELX-responsive *CFTR* mutation based on *in vitro* FRT data. After a median follow-up of 1.31 year, the mean change in $ppFEV_1$ was 4.53% (95% CI: 3.5, 5.56). Almost all subgroups according to *CFTR* mutation that included ≥5 patients showed an improvement in $ppFEV_1$ over that time, except for the subgroup with R74W.

Paediatric population

Paediatric patients aged 6 to <12 years

Study 445-106
In study 445-106 the primary endpoint of safety and tolerability was evaluated through 24 weeks in patients aged 6 to less than 12 years. Secondary endpoints were evaluation of pharmacokinetics and efficacy.

See Table 12 for a summary of secondary efficacy outcomes.

Table 12: Secondary efficacy analyses, full analysis set (N=66) (study 445-106)			
Analysis	**Baseline Mean (SD)**	**Absolute change through week 12 Within-group change (95% CI)**	**Absolute change through week 24 Within-group change (95% CI)***
$ppFEV_1$ (percentage points)	n=62 88.8 (17.7)	n=59 9.6 (7.3, 11.9)	n=59 10.2 (7.9, 12.6)
CFQ-R respiratory domain score (points)	n=65 80.3 (15.2)	n=65 5.6 (2.9, 8.2)	n=65 7.0 (4.7, 9.2)
BMI-for-age z-score	n=66 -0.16 (0.74)	n=58 0.22 (0.13, 0.30) †	n=33 0.37 (0.26, 0.48) ‡
Weight-for-age z-score	n=66 -0.22 (0.76)	n=58 0.13 (0.07, 0.18) †	n=33 0.25 (0.16, 0.33) ‡
Height-for-age z-score	n=66 -0.11 (0.98)	n=58 -0.03 (-0.06, 0.00) †	n=33 -0.05 (-0.12, 0.01) ‡
Number of pulmonary exacerbations††	N/A	N/A	n=66 4 (0.12) §
$LCI_{2.5}$	n=53 9.77 (2.68)	n=48 -1.83 (-2.18, -1.49)	n=50 -1.71 (-2.11, -1.30)

SD: Standard Deviation; CI: Confidence Interval; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: Body Mass Index; N/A: Not Applicable; LCI: Lung Clearance Index; n: size of subsample

* Not all participants included in the analyses had data available for all follow-up visits, especially from week 16 onwards. The ability to collect data at week 24 was hampered by the COVID-19 pandemic. Week 12 data were less impacted by the pandemic.

† At week 12 assessment.

‡ At week 24 assessment.

†† 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

Study 445-107 is 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 IVA/TEZ/ELX in patients who completed study 445-106. Efficacy endpoints were included as secondary endpoints. The final analysis of this study was conducted in 64 paediatric patients aged 6 years and older. With 192 additional weeks of treatment, sustained improvements in $ppFEV_1$, SwCl, CFQ-R RD score, and $LCI_{2.5}$ were shown, consistent with the results observed in the study 445-106.

Study 445-116

In study 445-116 treatment with IVA/TEZ/ELX in combination with IVA in patients aged 6 to less than 12 years resulted in statistically significant improvement through 24 weeks in the primary endpoint ($LCI_{2.5}$). The LS mean treatment difference for the IVA/TEZ/ELX in combination with IVA group versus placebo for the absolute change in $LCI_{2.5}$ from baseline through week 24 was -2.26 (95% CI: -2.71, -1.81; $P < 0.0001$).

Study 445-124

In study 445-124 the safety and efficacy of IVA/TEZ/ELX in patients with CF aged 6 years and older without an *F508del* mutation were evaluated. A post-hoc efficacy analysis was conducted in 31 patients

aged 6-12 years, of whom 23 patients received IVA/TEZ/ELX. The mean change (SD) from baseline was 10.2% (16.2) for $ppFEV_1$ and -37.7 (18.8) mmol/L for sweat chloride.

The European Medicines Agency has deferred the obligation to submit the results of studies with IVA/TEZ/ELX in combination with IVA in one or more subset of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ELX, TEZ and IVA are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of ELX and TEZ and twice-daily dosing of IVA, plasma concentrations of ELX, TEZ and IVA reach steady state within approximately 7 days for ELX, within 8 days for TEZ, and within 3-5 days for IVA. Upon dosing IVA/TEZ/ELX to steady state, the accumulation ratio is approximately 3.6 for ELX, 2.8 for TEZ and 4.7 for IVA. Key pharmacokinetic parameters for ELX, TEZ and IVA at steady state in patients with CF aged 12 years and older are shown in Table 13.

Table 13: Mean (SD) pharmacokinetic parameters of ELX, TEZ and IVA at steady state in patients with CF aged 12 years and older

Dose	Active Substance	C_{max} (µg/mL)	$AUC_{0-24h, ss}$ or $AUC_{0-12h, ss}$ (µg·h/mL)*
IVA 150 mg every 12 hours/TEZ 100 mg and ELX 200 mg once daily	ELX	9.15 (2.09)	162 (47.5)
	TEZ	7.67 (1.68)	89.3 (23.2)
	IVA	1.24 (0.34)	11.7 (4.01)

SD: Standard Deviation; C_{max}: maximum observed concentration; AUC_{ss}: Area Under the Concentration versus time curve at steady state
* AUC_{0-24h} for ELX and TEZ and AUC_{0-12h} for IVA.

Absorption

The absolute bioavailability of ELX when administered orally in the fed state is approximately 80%. ELX 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 TEZ and IVA is approximately 3 hours (2 to 4 hours) and 4 hours (3 to 6 hours), respectively. ELX exposure (AUC) increases approximately 1.9- to 2.5-fold when administered with a moderate-fat meal relative to fasted conditions. IVA 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 TEZ (see section 4.2).

As exposures of ELX were approximately 20% lower after administration of the IVA/TEZ/ELX granules relative to the reference IVA/TEZ/ELX tablet, the formulations are not considered interchangeable.

Distribution

ELX is >99% bound to plasma proteins and TEZ is approximately 99% bound to plasma proteins, in both cases primarily to albumin. IVA 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 IVA/TEZ/ELX in combination with IVA, the mean (±SD) apparent volume of distribution of ELX, TEZ and IVA was 53.7 L (17.7), 82.0 L (22.3) and 293 L (89.8), respectively. ELX, TEZ and IVA do not partition preferentially into human red blood cells.

Biotransformation

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

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

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

The effect of the CYP3A4*22 heterozygous genotype on TEZ, IVA and ELX exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. No dose-adjustment of TEZ, IVA or ELX is considered necessary. The effect in CYP3A4*22 homozygous genotype patients is expected to be stronger. However, no data are available for such patients.

Elimination

Following multiple dosing in the fed state, the mean (±SD) apparent clearance values of ELX, TEZ and IVA 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 ELX, TEZ and IVA following administration of the IVA/TEZ/ELX 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-life of TEZ following administration of the IVA/TEZ/ELX fixed-dose combination tablets is 11.9 (3.79) hours.

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

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

For ELX, TEZ and IVA there was negligible urinary excretion of unchanged medicine.

Hepatic impairment

ELX alone or in combination with TEZ and IVA has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of ELX, TEZ and IVA for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had an approximately 25% higher AUC and a 12% higher C_{max} for ELX, 73% higher AUC and a 70% higher C_{max} for M23-ELX, 20% higher AUC but similar C_{max} for TEZ, 22% lower AUC and a 20% lower C_{max} for M1-TEZ, and a 1.5-fold higher AUC and a 10% higher C_{max} for IVA compared with healthy subjects matched for demographics. The effect of moderately impaired hepatic function on total exposure (based

on summed values of ELX and its M23-ELX metabolite) was 36% higher AUC and a 24% higher C_{max} compared with healthy subjects matched for demographics (see sections 4.2, 4.4, and 4.8).

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

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

Renal impairment

ELX alone or in combination with TEZ and IVA has not been studied in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) less than 30 mL/min] or in patients with end-stage renal disease.

In human pharmacokinetic studies of ELX, TEZ and IVA, there was minimal elimination of ELX, TEZ and IVA in urine (only 0.23%, 13.7% [0.79% as unchanged medicine] and 6.6% of total radioactivity, respectively).

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

In population PK analysis conducted in 817 patients administered TEZ alone or in combination with IVA in phase 2 or phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min) did not affect the clearance of TEZ significantly (see sections 4.2 and 4.4).

Gender

The pharmacokinetic parameters of ELX (244 males compared to 174 females), TEZ and IVA are similar in males and females.

Race

Race had no clinically meaningful effect on ELX exposure based on population PK analysis in whites (N=373) and non-whites (N=45). The non-white races consisted of 30 Blacks or African Americans, 1 with multiple racial background and 14 with other ethnic background (no Asians).

Very limited PK data indicate comparable exposure of TEZ in whites (N=652) and non-whites (N=8). The non-white races consisted of 5 Blacks or African Americans and 3 Native Hawaiians or other Pacific Islanders.

Race had no clinically meaningful effect on the PK of IVA in whites (N=379) and non-whites (N=29) based on a population PK analysis. The non-white races consisted of 27 African Americans and 2 Asians.

Elderly

Clinical trials of IVA/TEZ/ELX in combination with IVA did not include sufficient number of patients aged 65 years and older to determine whether response in these patients is different from younger adults (see sections 4.2 and 4.4).

Paediatric population

ELX, TEZ and IVA exposures observed in phase 3 studies as determined using population PK analysis are presented by age group in Table 14. Exposures of ELX, TEZ and IVA in patients aged 2 to less than 18 years are within the range observed in patients aged 18 years and older.

Table 14: Mean (SD) ELX, M23-ELX, TEZ, M1-TEZ and IVA exposures observed at steady state by age group and dose administered

Age/Weight group	Dose	ELX $AUC_{0-24h, ss}$ (µg·h/mL)	M23-ELX $AUC_{0-24h, ss}$ (µg·h/mL)	TEZ $AUC_{0-24h, ss}$ (µg·h/mL)	M1-TEZ $AUC_{0-24h, ss}$ (µg·h/mL)	IVA $AUC_{0-12h, ss}$ (µg·h/mL)
Patients aged 2 to <6 years, 10 kg to 14 kg (N=16)	IVA 60 mg qAM/ TEZ 40 mg qd/ ELX 80 mg qd and IVA 59.5 mg qPM	128 (24.8)	56.5 (29.4)	87.3 (17.3)	194 (24.8)	11.9 (3.86)
Patients aged 2 to <6 years, ≥14 kg (N=59)	IVA 75 mg q12h/ TEZ 50 mg qd/ ELX 100 mg qd	138 (47.0)	59.0 (32.7)	90.2 (27.9)	197 (43.2)	13.0 (6.11)
Patients aged 6 to 12 years, <30 kg (N=36)	IVA 75 mg q12h/ TEZ 50 mg qd/ ELX 100 mg qd	116 (39.4)	45.4 (25.2)	67.0 (22.3)	153 (36.5)	9.78 (4.50)
Patients aged 6 to 12 years, ≥30 kg (N=30)	IVA 150 mg q12h/TEZ 100 mg qd/ ELX 200 mg qd	195 (59.4)	104 (52.0)	103 (23.7)	220 (37.5)	17.5 (4.97)
Adolescent patients (12 to <18 years) (N=72)	IVA 150 mg q12h/ TEZ 100 mg qd/ ELX 200 mg qd	147 (36.8)	58.5 (25.6)	88.8 (21.8)	148 (33.3)	10.6 (3.35)
Adult patients (≥18 years) (N=179)	IVA 150 mg q12h/ TEZ 100 mg qd/ ELX 200 mg qd	168 (49.9)	64.6 (28.9)	89.5 (23.7)	128 (33.7)	12.1 (4.17)

SD: Standard Deviation; AUC_{ss}: Area Under the Concentration versus time curve at steady state; qd: once-daily; qAM: once each morning; qPM: once each evening; q12h: once every 12 hours

5.3 Preclinical safety data

Elexacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility and pregnancy
The No Observed Adverse Effect Level (NOAEL) for fertility findings was 55 mg/kg/day (2 times the maximum recommended human dose (MRHD) based on summed AUCs of ELX and its metabolite) in male rats and 25 mg/kg/day (4 times the MRHD based on summed AUCs of ELX and its metabolite) in female rats. In rat, at doses exceeding the maximum tolerated dose (MTD), degeneration and atrophy of seminiferous tubules are correlated to oligo-/aspermia and cellular debris in epididymides. In dog testes, minimal or mild, bilateral degeneration/atrophy of the seminiferous tubules was present in males administered 14 mg/kg/day ELX (15 times the MRHD based on summed AUCs of ELX and its metabolite) that did not resolve during the recovery period, however without further sequelae. The human relevance of these findings is unknown.

ELX was not teratogenic in rats at 40 mg/kg/day and at 125 mg/kg/day in rabbits (approximately 9 and 4 times, respectively, the MRHD based on summed AUCs of ELX and its metabolite [for rat] and AUC of ELX [for rabbit]) with developmental findings being limited to lower mean foetal body weight at ≥25 mg/kg/day.

Placental transfer of ELX was observed in pregnant rats.

Tezacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Placental transfer of TEZ was observed in pregnant rats.

Juvenile toxicity studies in rats exposed during postnatal day 7 to 35 (PND 7-35) showed mortality and moribundity, even at low doses. Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period. Exposure in rats from PND 21-49 did not show toxicity at the highest dose which was approximately two times the intended human exposure. Tezacaftor and its metabolite, M1-TEZ, are substrates for P-glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are likely not relevant for the indicated paediatric population of 2 years of age and older, for whom P-glycoprotein expression levels are equivalent to levels observed in adults.

Ivacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility and pregnancy
The NOAEL for fertility findings was 100 mg/kg/day (5 times the MRHD based on summed AUCs of IVA and its metabolites) in male rats and 100 mg/kg/day (3 times the MRHD based on summed AUCs of IVA and its metabolites) in female rats.

In the pre- and post-natal study IVA decreased survival and lactation indices and caused a reduction in pup body weights. The NOAEL for viability and growth in the offspring provides an exposure level of

approximately 3 times the systemic exposure of IVA and its metabolites in adult humans at the MRHD. Placental transfer of IVA was observed in pregnant rats and rabbits.

Juvenile animal studies
Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through day 35 at IVA exposure levels of 0.21 time the MRHD based on systemic exposure of IVA and its metabolites. This finding has not been observed in foetuses derived from rat dams treated with IVA on gestation days 7 to day 17, in rat pups exposed to IVA through milk ingestion up to postnatal day 20, in 7-week-old rats, nor in 3.5- to 5-month-old dogs treated with IVA. The potential relevance of these findings in humans is unknown (see section 4.4).

Ivacaftor/tezacaftor/elexacaftor

Combination repeat-dose toxicity studies in rats and dogs involving the co-administration of ELX, TEZ and IVA to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions. The potential for synergistic toxicity on male reproduction has not been assessed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose (E464)
Hypromellose acetate succinate
Sodium laurilsulfate (E487)
Croscarmellose sodium (E468)
Microcrystalline cellulose (E460(i))
Magnesium stearate (E470b)

Tablet film coat

Hypromellose (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets

4 years

Kaftrio 75 mg/50 mg/100 mg film-coated tablets

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Pack size of 56 tablets (4 blister cards, each with 14 tablets).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001
EU/1/20/1468/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 August 2020
Date of latest renewal: 22 May 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 60 mg/40 mg/80 mg granules in sachet
Kaftrio 75 mg/50 mg/100 mg granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kaftrio 60 mg/40 mg/80 mg granules in sachet

Each sachet contains 60 mg of ivacaftor, 40 mg of tezacaftor and 80 mg of elexacaftor.

Excipient with known effect

Each sachet contains 188.6 mg of lactose monohydrate.

Kaftrio 75 mg/50 mg/100 mg granules in sachet

Each sachet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

Excipient with known effect

Each sachet contains 235.7 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules in sachet (granules)

White to off-white granules approximately 2 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Kaftrio should only be prescribed by healthcare professionals 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 at least one *CFTR* mutation that is responsive based on clinical and/or *in vitro* data (using a genotype assay) (see section 5.1). Kaftrio should only be used in patients diagnosed with CF. A diagnosis of CF should be made based on diagnostic guidelines and clinical judgement.

There are a limited number of patients who harbour mutations not listed in Table 5 that may be responsive to Kaftrio. In these cases, Kaftrio can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision. This excludes patients with two Class I

(null) mutations (mutations that are known not to produce CFTR protein) as they are not expected to respond to modulator therapy (see sections 4.1, 4.4, and 5.1).

Monitoring of transaminases (ALT and AST) and total bilirubin is recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered (see section 4.4).

Posology

Paediatric patients aged 2 to less than 6 years should be dosed according to Table 1.

Table 1: Dosing recommendations for patients aged 2 to less than 6 years

Age	Weight	Morning dose	Evening dose
2 to less than 6 years	10 kg to < 14 kg	One sachet of ivacaftor 60 mg/tezacaftor 40 mg/elexacaftor 80 mg granules	One sachet of ivacaftor 59.5 mg granules
	≥ 14 kg	One sachet of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg granules	One sachet of ivacaftor 75 mg granules

The morning and evening dose should be taken approximately 12 hours apart, with fat-containing food (see Method of administration).

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.
  OR
- 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.

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 2 (see sections 4.4 and 4.5).

Table 2: Dosing schedule for concomitant use with moderate and strong CYP3A inhibitors

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
2 years to less than 6 years	10 kg to < 14 kg	Alternate each day: • One sachet of ivacaftor 60 mg/ tezacaftor 40 mg/elexacaftor 80 mg granules on the first day • One sachet of ivacaftor 59.5 mg granules on the next day	One sachet of ivacaftor 60 mg/ tezacaftor 40 mg/ elexacaftor 80 mg granules twice a week, approximately 3 to 4 days apart. No evening sachet of ivacaftor granules.

		No evening sachet of ivacaftor granules.	
2 years to less than 6 years	≥ 14 kg	Alternate each day: • One sachet of ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg granules on the first day • One sachet of ivacaftor 75 mg granules on the next day No evening sachet of ivacaftor granules.	One sachet of ivacaftor 75 mg/ tezacaftor 50 mg/ elexacaftor 100 mg granules twice a week, approximately 3 to 4 days apart. No evening sachet of ivacaftor granules.

Special populations

Hepatic impairment
Treatment of patients aged 2 to less than 6 years with moderate hepatic impairment (Child-Pugh Class B) is not recommended. For patients aged 2 to less than 6 years with moderate hepatic impairment, the use of Kaftrio should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose (see Table 3).

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 Kaftrio.

No dose adjustment is recommended for patients with mild (Child-Pugh Class A) hepatic impairment (see Table 3) (see sections 4.4, 4.8, and 5.2).

Table 3: Recommendation for use in patients aged 2 to less than 6 years with hepatic impairment

Age	Weight	Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
2 years to less than 6 years	10 kg to < 14 kg	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, Kaftrio should be used with caution at a reduced dose, as follows: • Days 1-3: one sachet of ivacaftor 60 mg/ tezacaftor 40 mg/elexacaftor 80 mg granules each day • Day 4: no dose • Days 5-6: one sachet of ivacaftor 60 mg/ tezacaftor 40 mg/elexacaftor 80 mg granules each day • Day 7: no dose Repeat above dosing schedule each week.	Should not be used

			The evening dose of the ivacaftor granules should not be taken.	
2 years to less than 6 years	≥ 14 kg	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, Kaftrio should be used with caution at a reduced dose, as follows: • Days 1-3: one sachet of ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg granules each day • Day 4: no dose • Days 5-6: one sachet of ivacaftor 75 mg/ tezacaftor 50 mg/elexacaftor 100 mg granules each day • Day 7: no dose Repeat above dosing schedule each week. The evening dose of the ivacaftor granules should not be taken.	Should not be used

Renal impairment
No dose adjustment is recommended for patients with mild and moderate renal impairment. There is no experience in patients with severe renal impairment or end-stage renal disease (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Kaftrio in combination with ivacaftor (IVA) in children aged less than 2 years have not yet been established. No data are available.

Method of administration

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, water, milk, or juice. A fat-containing meal or snack should be consumed just before or after dosing.

Kaftrio should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats (see section 5.2).

Food or drink containing grapefruit should be avoided during treatment with Kaftrio (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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. In clinical studies, elevated transaminases were more frequently observed in patients treated with IVA/TEZ/ELX in combination with IVA compared to placebo. In patients taking IVA/TEZ/ELX in combination with IVA, these elevations have sometimes 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 treatment, every 3 months during the first year of treatment and annually thereafter (see section 4.2).

For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt treatment and promptly measure serum transaminases and total bilirubin if a patient develops clinical signs or symptoms of liver injury. Interrupt dosing in the event of ALT or AST >5 × the upper limit of normal (ULN), or ALT or AST >3 × ULN with total bilirubin >2 × ULN. Closely monitor the laboratory tests until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment. Patients who resume treatment after interruption should be monitored closely.

In patients with pre-existing advanced liver disease, IVA/TEZ/ELX in combination with IVA should be used with caution and only if the benefits are expected to outweigh the risks (see sections 4.2, 4.8, and 5.2).

Hepatic impairment

Treatment of patients with moderate hepatic impairment is not recommended. For patients with moderate hepatic impairment, the use of IVA/TEZ/ELX should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose (see Table 3).

Patients with severe hepatic impairment should not be treated with IVA/TEZ/ELX (see sections 4.2, 4.8, and 5.2).

Depression

Depression (including suicidal ideation and suicide attempt) has been reported in patients treated with IVA/TEZ/ELX, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders (see section 4.8). In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, unusual changes in behaviour, anxiety, or insomnia and to seek medical advice immediately if these symptoms present.

Paediatric population
In young children (aged 2-5 years) treated with IVA/TEZ/ELX behavioural changes have been reported, which occurred usually within the first two months of treatment initiation. In some cases, symptom improvement was reported after treatment discontinuation.

Renal impairment

There is no experience in patients with severe renal impairment/end-stage renal disease therefore caution is recommended in this population (see sections 4.2 and 5.2).

Mutations unlikely to respond to modulator therapy

Patients with a genotype consisting of two *CFTR* mutations that are known not to produce CFTR protein (i.e., two Class I mutations) are not expected to respond to Kaftrio treatment.

Clinical studies comparing IVA/TEZ/ELX to TEZ/IVA or IVA

No clinical study has been conducted to directly compare IVA/TEZ/ELX to TEZ/IVA or IVA in patients not harbouring *F508del* variants.

Patients after organ transplantation

IVA/TEZ/ELX in combination with IVA 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 for interactions with commonly used immunosuppressants.

Rash events

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 IVA/TEZ/ELX was continued and the rash resolved without treatment. Children have a higher incidence rate compared to adults. The incidence of rash events was also higher in females compared to males, particularly in females taking hormonal contraceptives (see section 4.8). A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, interrupting treatment with IVA/TEZ/ELX in combination with IVA and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming IVA/TEZ/ELX in combination with IVA without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered (see section 4.8).

Elderly

Clinical studies of IVA/TEZ/ELX in combination with IVA did not include sufficient number of patients aged 65 years and older to determine whether response in these patients is different from younger adults. Dose recommendations are based on the pharmacokinetic profile and knowledge from studies with tezacaftor/ivacaftor (TEZ/IVA) in combination with IVA, and IVA monotherapy (see section 5.2).

Interactions with medicinal products

CYP3A inducers
Exposure to IVA is significantly decreased and exposures to ELX and TEZ are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduced efficacy of IVA/TEZ/ELX and IVA; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors
Exposures of ELX, TEZ and IVA are increased when co-administered with strong or moderate CYP3A inhibitors. The dose of IVA/TEZ/ELX and IVA should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see section 4.5 and Table 2 in section 4.2).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with IVA-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 IVA cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with IVA/TEZ/ELX in combination with IVA (see section 5.3).

Excipients with known effect

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products affecting the pharmacokinetics of ELX, TEZ and/or IVA

CYP3A inducers
ELX, TEZ and IVA are substrates of CYP3A (IVA is a sensitive substrate of CYP3A). Concomitant use of strong CYP3A inducers may result in reduced exposures and thus reduced IVA/TEZ/ELX efficacy. Co-administration of IVA with rifampicin, a strong CYP3A inducer, significantly decreased IVA area under the curve (AUC) by 89%. ELX and TEZ exposures are also expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.4).

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 ELX AUC by 2.8-fold and TEZ AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, IVA AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of IVA/TEZ/ELX and IVA should be reduced when co-administered with strong CYP3A inhibitors (see Table 2 in section 4.2 and section 4.4).

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole and voriconazole
- telithromycin and clarithromycin

Simulations indicated that co-administration with moderate CYP3A inhibitors fluconazole, erythromycin and verapamil, may increase ELX and TEZ AUC by approximately 1.9- to 2.3-fold. Co-administration of fluconazole increased IVA AUC by 2.9-fold. The dose of IVA/TEZ/ELX and IVA should be reduced when co-administered with moderate CYP3A inhibitors (see Table 2 in section 4.2 and section 4.4).

Examples of moderate CYP3A inhibitors include:
- fluconazole
- erythromycin

Co-administration with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ELX, TEZ and IVA. Food or drink containing grapefruit should be avoided during treatment with IVA/TEZ/ELX and IVA (see section 4.2).

Ciprofloxacin

ELX/TEZ/IVA was not evaluated for concomitant use with ciprofloxacin. However, ciprofloxacin had no clinically relevant effect on the exposure of TEZ or IVA and is not expected to have a clinically relevant effect on the exposure of ELX. Therefore, no dose adjustment is necessary during concomitant administration of IVA/TEZ/ELX with ciprofloxacin.

Potential for interaction with transporters

In vitro studies showed that ELX is a substrate for the efflux transporters P-gp and Breast Cancer Resistance Protein (BCRP) but is not a substrate for OATP1B1 or OATP1B3. Exposure to ELX is not expected to be affected significantly by concomitant use of P-gp and BCRP inhibitors due to its high intrinsic permeability and low likelihood of being excreted intact.

In vitro studies showed that TEZ is a substrate for the uptake transporter OATP1B1 and efflux transporters P-gp and BCRP. TEZ is not a substrate for OATP1B3. Exposure to TEZ is not expected to be affected significantly by concomitant inhibitors of OATP1B1, P-gp, or BCRP due to its high intrinsic permeability and low likelihood of being excreted intact. However, exposure to M2-TEZ (TEZ metabolite) may be increased by inhibitors of P-gp. Therefore, caution should be used when P-gp inhibitors (e.g., ciclosporin) are used with IVA/TEZ/ELX.

In vitro studies showed that IVA is not a substrate for OATP1B1, OATP1B3, or P-gp. IVA and its metabolites are substrates of BCRP *in vitro*. Due to its high intrinsic permeability and low likelihood of being excreted intact, co-administration of BCRP inhibitors is not expected to alter exposure of IVA and M1-IVA, while any potential changes in M6-IVA exposures are not expected to be clinically relevant.

<u>Medicinal products affected by ELX, TEZ and/or IVA</u>

CYP2C9 substrates

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

Potential for interaction with transporters

Co-administration of IVA or TEZ/IVA with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by IVA. Administration of IVA/TEZ/ELX and IVA 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.

ELX and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. TEZ/IVA increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration with IVA/TEZ/ELX in combination with IVA 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 ELX and M23-ELX.

ELX and IVA are inhibitors of BCRP. Co-administration of IVA/TEZ/ELX, and IVA may increase exposures of medicinal products that are substrates of BCRP, such as rosuvastatin. When used concomitantly with substrates of BCRP, appropriate monitoring should be used.

Hormonal contraceptives

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of ELX, TEZ, or IVA in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of IVA/TEZ/ELX during pregnancy.

Breast-feeding

Limited data show that ELX, TEZ, and IVA are excreted in human milk and have been quantified in plasma of breastfed newborns/infants of treated women. There is insufficient information on the effects of IVA/TEZ/ELX in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from IVA/TEZ/ELX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of ELX, TEZ and IVA on fertility in humans. TEZ had no effects on fertility and reproductive performance indices in male and female rats at clinically relevant exposures. ELX and IVA had an effect on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

IVA/TEZ/ELX in combination with IVA has a minor influence on the ability to drive or use machines. Dizziness has been reported in patients receiving IVA/TEZ/ELX in combination with IVA, TEZ/IVA in combination with IVA as well as IVA (see section 4.8). Patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions experienced by patients aged 12 years and older who received IVA/TEZ/ELX in combination with IVA were headache (17.3%), diarrhoea (12.9%), upper respiratory tract infection (11.9%) and aminotransferase increased (10.9%).

Serious adverse reactions of rash experienced by patients aged 12 years and older were reported in 1.5% patients treated with IVA/TEZ/ELX in combination with IVA (see section 4.4).

Tabulated list of adverse reactions

Table 4 reflects adverse reactions observed with IVA/TEZ/ELX in combination with IVA, TEZ/IVA in combination with IVA, and IVA monotherapy. Adverse reactions are listed by MedDRA system organ class and frequency: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions		
MedDRA System Organ Class	**Adverse Reactions**	**Frequency**
Infections and infestations	Upper respiratory tract infection*, Nasopharyngitis	very common
	Rhinitis*, Influenza*	common
Immune system disorders	Hypersensitivity	not known
Metabolism and nutrition disorders	Hypoglycaemia*	common
Psychiatric disorders	Depression, Behavioural changes	not known
Nervous system disorders	Headache*, Dizziness*	very common
Ear and labyrinth disorders	Ear pain, Ear discomfort, Tinnitus, Tympanic membrane hyperaemia, Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain, Nasal congestion*	very common
	Rhinorrhoea*, Sinus congestion, Pharyngeal erythema, Abnormal breathing*	common
	Wheezing*	uncommon
Gastrointestinal disorders	Diarrhoea*, Abdominal pain*	very common
	Nausea, Abdominal pain upper*, Flatulence*	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*	very common
	Aspartate aminotransferase increased*	very common
	Liver injury†, Total bilirubin increase†	not known
Skin and subcutaneous tissue disorders	Rash*	very common
	Acne*, Pruritus*	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation, Gynaecomastia, Nipple disorder, Nipple pain	uncommon
Investigations	Bacteria in sputum, Blood creatine phosphokinase increased*	very common
	Blood pressure increased*	uncommon
*Adverse reactions observed during clinical studies with IVA/TEZ/ELX in combination with IVA. †Liver injury (ALT and AST and total bilirubin increase) reported from post-marketing data with IVA/TEZ/ELX in combination with IVA. Frequency cannot be estimated from the available data.		

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 aged 12 years and older (study 445-103).
- A 192-week, open-label safety and efficacy study (study 445-105) in 506 patients who rolled over from studies 445-102 and 445-103.
- An 8-week, randomised, double-blind, active-controlled study in 258 patients aged 12 years and older (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, randomised, placebo-controlled study (study 445-116) in 121 patients aged 6 to less than 12 years.

- A 192-week, two-part (part A and part B), open-label safety and efficacy study (study 445-107) in 64 patients aged 6 years and older who rolled over from study 445-106.
- A 24-week, open-label study (study 445-111) in 75 patients aged 2 to less than 6 years.
- A 24-week, randomised, double-blind, placebo-controlled study (study 445-124) in 307 patients aged 6 years and older.

Description of selected adverse reactions

Transaminase elevations
In study 445-102, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 × the ULN was 1.5%, 2.5% and 7.9% in IVA/TEZ/ELX-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 IVA/TEZ/ELX-treated patients and 4.0% in placebo-treated patients.

During the open-label studies, some patients discontinued treatment due to elevated transaminases. Post-marketing cases of treatment discontinuation due to elevated transaminases have been reported (see section 4.4).

Rash events
Studies in IVA/TEZ/ELX-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 IVA/TEZ/ELX-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients. In patients treated with IVA/TEZ/ELX, 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).

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 IVA/TEZ/ELX was continued and the rash resolved without treatment.

Increased creatine phosphokinase
In study 445-102, the incidence of maximum creatine phosphokinase >5 × the ULN was 10.4% in IVA/TEZ/ELX- and 5.0% in placebo-treated patients. The observed creatine phosphokinase elevations were generally transient and asymptomatic and many were preceded by exercise.

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 IVA/TEZ/ELX-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%, respectively in IVA/TEZ/ELX-treated patients compared with 3.5% and 3.5%, respectively in placebo-treated patients.

Paediatric population

The safety data of IVA/TEZ/ELX in combination with IVA in studies 445-102, 445-103, 445-104, 445-106, 445-111, and 445-124 and was evaluated in 272 patients between 2 to less than 18 years of age. The safety profile is generally consistent among paediatric and adult patients.

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 × ULN were 0.0%, 1.5%, and 10.6%, respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

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 × ULN were 1.3%, 2.7%, and 8.0% respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

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.

Lenticular opacity
One patient had an adverse event of lenticular opacity.

Behavioural changes
Most cases of behavioural changes have been reported in younger children aged 2-5 years.

Other special populations

With the exception of sex differences in rash, the safety profile of IVA/TEZ/ELX in combination with IVA was generally similar across all subgroups of patients, including analysis by age, baseline percent predicted forced expiratory volume in one second ($ppFEV_1$) and geographic regions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

ELX and TEZ 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 CFTR to increase the amount of CFTR

protein delivered to the cell surface compared to either molecule alone. IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of ELX, TEZ and IVA is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

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

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

In CF, the presence of one *CFTR* mutation responsive to IVA/TEZ/ELX based on *in vitro* data in FRT cells, will likely result in a clinical response.

Table 5 lists *CFTR* mutations included in the indication for treatment with Kaftrio. The occurrence of *CFTR* mutations listed in this table should not be used in lieu of a diagnosis of cystic fibrosis, nor as a sole determinant for prescribing purposes.

Table 5: *CFTR* mutations identified to be responsive to IVA/TEZ/ELX based on clinical and/or *in vitro* data

293A→G	E264V	H939R	N1088D	S108F
314del9	E282D	H939R;H949L[‡]	N1195T	S158N
546insCTA	E292K	H954P	N1303I	S182R
548insTAC	E384K	H1054D	N1303K[*]	S308P
711+3A→G[*]	E403D	H1079P	P5L[†]	S341P
1140-1151dup	E474K	H1085P	P67L[*]	S364P
1461insGAT	E527G	H1085R	P111L	S434P
1507_1515del9	E588V	H1375N	P140S	S492F
2055del9	E822K	H1375P	P205S	S519G
2183A→G	E831X	I86M	P439S	S531P
2789+5G→A[*]	E1104K	I105N	P499A	S549I
2851A/G	E1104V	I125T	P574H	S549N
3007del6	E1126K	I148L	P750L	S549R[*]
3132T→G	E1221V	I148N	P798S	S557F
3141del9	E1228K	I175V	P988R	S589I
3143del9	E1409K	I331N	P1013H	S589N
3272-26A→G[*†]	E1433K	I336K	P1013L	S624R
3331del6	F87L	I336L	P1021L	S686Y
3410T→C	F191V	I444S	P1021T	S737F
3523A→G	F200I	I497S	P1372T	S821G
3601A→C	F311del	I502T	Q30P	S898R
3761T→G	F311L	I506L	Q98P	S912L
3791C/T	F312del	I506V	Q98R	S912L;G1244V[‡]
3849+10kbC→T[*†]	F433L	I506V;D1168G[‡]	Q151K	S912T
3850G→A	F508C;S1251 N[‡]	I521S	Q179K	S945L[*†]
3978G→C	F508del[*]	I530N	Q237E	S955P

A46D	F508del;R1438W‡	I556V	Q237H	S977F
A62P	F575Y	I586V	Q237P	S977F;R1438W‡
A107G	F587I	I601F	Q359K;T360K‡	S1045Y
A120T	F587L	I618N	Q359R	S1118F
A141D	F693L(TTG)	I618T	Q372H	S1159F
A155P	F932S	I980K	Q493L	S1159P
A234D	F1016S	I1023R	Q493R	S1188L
A234V	F1052V	I1139V	Q552P	S1251N
A238V	F1074L	I1203V	Q1012P	S1255P
A309D	F1078S	I1234L	Q1209P	T338I
A349V	F1099L	I1234V	Q1291H	T351I
A357T	F1107L	I1269N	Q1291R	T351S
A455E*†	G27E	I1366N	Q1313K	T351S;R851L‡
A455V	G27R	I1366T	Q1352H	T388M
A457T	G126D	K162E	R31L	T465I
A462P	G178E	K464E	R74Q	T501A
A534E	G178R	K464N	R74Q;R297Q‡	T582S
A554E	G194R	K522E	R74Q;V201M;D1270N‡	T908N
A566D	G194V	K522Q	R74W	T990I
A872E	G213E	K951E	R74W;D1270N‡	T1036N*
A1006E	G213E;R668C‡	K1060T	R74W;R1070W;D1270N‡	T1057R
A1025D	G213V	L15P	R74W;S945L‡	T1086A
A1067P	G226R	L15P;L1253F‡	R74W;V201M‡	T1086I
A1067T	G239R	L32P	R74W;V201M;D1270N‡	T1246I
A1067V	G253R	L88S	R74W;V201M;L997F‡	T1299I
A1081V	G314E	L102R;F1016S‡	R75L	T1299K
A1087P	G314R	L137P	R75Q;L1065P‡	V11I
A1319E	G424S	L159S	R75Q;N1088D‡	V93D
A1374D	G437D	L165S	R75Q;S549N‡	V201M
A1466S	G461R	L167R	R117C†	V232A
C225R	G461V	L206W*†	R117C;G576A;R668C‡	V232D
C491R	G463V	L210P	R117G	V317A
C590Y	G480C	L293P	R117H*	V322M
C866Y	G480D	L327P	R117L	V392G
c.1367_1369dupTTG	G480S	L333F	R117L;L997F‡	V456A
D58H	G500D	L333H	R117P	V456F
D58V	G545R	L346P	R248K	V520I
D110E	G551A	L441P	R258G	V562I;A1006E‡
D110H	G551D*	L453S	R297Q	V562L
D110N	G551R	L467F	R334L	V591A
D192G	G551S	L558F	R334Q	V603F
D192N	G576A;R668C‡	L619S	R334W†	V920L
D373N	G576A;S1359Y‡	L633P	R347H*	V920M
D426N	G622D	L636P	R347L	V1008D
D443Y	G622V	L927P	R347P	V1010D
D443Y;G576A;R668C‡	G628A	L967F;L1096R‡	R352Q	V1153E
D529G	G628R	L973F	R352W	V1240G
D565G	G85E*†	L1011S	R516S	V1293G
D567N	G930E	L1065R	R553Q	V1293I
D579G	G970D	L1077P*†	R555G	V1415F
D614G	G970S	L1227S	R600S	W202C
D651H	G970V	L1324P	R709Q	W361R

D651N	G1047D	L1335P	R751L	W496R
D806G	G1047R	L1388P	R792G	W1098C
D924N	G1061R	L1480P	R792Q	W1282G
D979A	G1069R	M150K	R810G	W1282R
D979V	G1123R	M150R	R851L	Y89C
D985H	G1173S	M152L	R933G	Y109H
D985Y	G1237V	M152V	R1048G	Y109N
D993A	G1244E	M265R	R1066C†	Y122C
D993G	G1244R	M348K	R1066G	Y161C
D993Y	G1247R	M394L	R1066H*†	Y161D
D1152A	G1249E	M469V	R1070P	Y161S
D1152H*†	G1249R	M498I	R1070Q	Y301C
D1270N*	G1265V	M952I	R1070W	Y563N
D1270Y	G1298V	M952T	R1162Q	Y913S
D1312G	G1349D	M961L	R1239S	Y919C
D1377H	G149R;G576A;R668C‡	M1101K*†	R1283G	Y1014C
D1445N	H139L	M1137R	R1283M	Y1032C
E56K	H139R	M1137V	R1283S	Y1032N
E60K	H146R	M1210K	R1438W	Y1073C
E92K	H199Q	N186K	S13F	Y1092H
E116K	H199Y	N187K	S13P	Y1381H
E116Q	H609L	N396Y	S18I	
E193K	H620P	N418S	S18N	
E217G	H620Q	N900K	S50P	

There are people with CF harbouring two rare, non-*F508del CFTR* mutations not listed in Table 5. Provided that they do not harbour two Class I (null) mutations (mutations that are known not to produce CFTR protein) (see section 4.1), they may respond to treatment. In these cases, Kaftrio can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision.

The individual diagnosis of CF should be based on diagnostic guidelines and clinical judgement as considerable variability exists in phenotype for patients harbouring the same genotype.

* Mutations supported by clinical data.
† Mutations supported by Real-World data in ≥ 5 patients.
‡ Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
Non-annotated mutations are included based on the FRT assay in which a positive response is indicative of a clinical response.

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 predicts either no production of a CFTR protein or a CFTR protein that does not transport chloride and is not responsive to other CFTR modulators [IVA and TEZ/IVA] *in vitro*), a reduction in sweat chloride was observed from baseline at week 4 and sustained through the 24-week treatment period. The treatment difference of IVA/TEZ/ELX in combination with IVA 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 IVA/TEZ/ELX in combination with IVA compared to TEZ/IVA in combination with IVA 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 mutation on the second allele with a gating defect or residual CFTR activity), the mean absolute change in sweat chloride from baseline through week 8 for the IVA/TEZ/ELX in combination with IVA group was -22.3 mmol/L (95% CI: -24.5, -20.2; $P < 0.0001$). The treatment difference of IVA/TEZ/ELX in combination with IVA compared to the control group (IVA group or TEZ/IVA in combination with IVA group) 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 (n=62) through week 24 (n=60) was -60.9 mmol/L (95% CI: -63.7, -58.2)*. The mean absolute change in sweat chloride from baseline through week 12 (n=59) was -58.6 mmol/L (95% CI: -61.1, -56.1).

* Not all participants included in the analyses had data available for all follow-up visits, especially from week 16 onwards. The ability to collect data at week 24 was hampered by the COVID-19 pandemic. Week 12 data were less impacted by the pandemic.

In study 445-116 (patients aged 6 to less than 12 years who are heterozygous for the *F508del* mutation and a minimal function mutation), treatment with IVA/TEZ/ELX in combination with IVA resulted in reduction in sweat chloride through week 24, as compared to placebo. The LS mean treatment difference for the IVA/TEZ/ELX in combination with IVA group versus placebo for absolute change in sweat chloride from baseline through week 24 was -51.2 mmol/L (95% CI: -55.3, -47.1; nominal $P < 0.0001$).

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*, IVA/TEZ/ELX-responsive *CFTR* mutation [see Table 6]), 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 ELX and 3 times the maximum recommended dose of TEZ and IVA, 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 IVA/TEZ/ELX-treated patients.

Clinical efficacy and safety

The efficacy of IVA/TEZ/ELX in combination with IVA in patients with CF was demonstrated in seven phase 3 studies. Patients enrolled in these studies were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a mutation with minimal function (MF), a gating defect, or residual CFTR activity on the second allele. Study 445-124 enrolled patients who had at least one qualifying non-*F508del,* IVA/TEZ/ELX-responsive *CFTR* mutation (see Table 6).

Study 445-102 was a 24-week, randomised, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and an MF mutation on the second allele. CF patients eligible for this study were required to either have Class I mutations that predicted no CFTR protein being produced (including nonsense mutations, canonical splice mutations and insertion/deletion frameshift mutations both small (≤3 nucleotide) and non-small (>3 nucleotide)), or missense mutations which results in CFTR protein that does not transport chloride and is not responsive to IVA and TEZ/IVA *in vitro*. The most frequent alleles with minimal function assessed in the study were *G542X*, *W1282X*, *R553X*, and *R1162X*; *621+1G→T*, *1717-1G→A*, and *1898+1G→A*; *3659delC*, and *394delTT*; *CFTRdele2,3*; and *N1303K*, *I507del*, *G85E*, *R347P*, and *R560T*. A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomised and dosed to receive placebo or IVA/TEZ/ELX in combination with IVA. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%).

Study 445-103 was a 4-week, randomised, double-blind, active-controlled study in patients who were homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received TEZ/IVA in combination with IVA during a 4-week open-label run-in period and were then randomised and dosed to receive either IVA/TEZ/ELX in combination with IVA or TEZ/IVA in combination with IVA 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 run-in period was 60.9% (range: 35.0%, 89.0%).

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

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 two IVA 37.5 mg/TEZ 25 mg/ELX 50 mg tablets in the morning and one IVA 75 mg tablet in the evening. Patients weighing ≥30 kg at baseline were administered two IVA 75 mg/TEZ 50 mg/ELX 100 mg tablets in the morning and one IVA 150 mg tablet in the evening. 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%).

Study 445-116 was a 24-week, randomised, double-blind, placebo-controlled study in patients aged 6 to less than 12 years (mean age at baseline 9.2 years) who were heterozygous for the *F508del* mutation and a minimal function mutation. A total of 121 patients were randomised to receive either placebo or IVA/TEZ/ELX in combination with IVA. Patients who received IVA/TEZ/ELX in combination with IVA weighing <30 kg at baseline were administered two IVA 37.5 mg/TEZ 25 mg/ELX 50 mg tablets in the morning and one IVA 75 mg tablet in the evening. Patients weighing ≥30 kg at baseline were administered two IVA 75 mg/TEZ 50 mg/ELX 100 mg tablets in the morning and one IVA 150 mg tablet in the evening. At screening, patients had a $ppFEV_1$ ≥70% [mean $ppFEV_1$ at baseline of 89.3% (range: 44.6%, 121.8%)], $LCI_{2.5}$ result ≥7.5 [mean $LCI_{2.5}$ at baseline of 10.01 (range: 6.91, 18.36)], and weighed ≥15 kg.

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). A total of 75 patients who are 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 IVA 60 mg/TEZ 40 mg/ELX 80 mg once

every morning and IVA 59.5 mg once every evening. Patients weighing ≥14 kg at baseline were administered IVA 75 mg every 12 hours/TEZ 50 mg qd/ELX 100 mg qd.

Study 445-124 was a 24-week, randomised, placebo-controlled, double-blind, parallel group study in patients aged 6 years and older. Patients who had at least one qualifying non-*F508del*, IVA/TEZ/ELX-responsive *CFTR* mutation (see Table 6) and did not have an exclusionary (other IVA/TEZ/ELX-responsive) mutation were eligible for the study.

Table 6: Eligible IVA/TEZ/ELX-responsive *CFTR* mutations				
2789+5G>A	*D1152H*	*L997F*	*R117C*	*T338I*
3272-26A>G	*G85E*	*M1101K*	*R347H*	*V232D*
3849+10kbC>T	*L1077P*	*P5L*	*R347P*	
A455E	*L206W*	*R1066H*	*S945L*	

A total of 307 patients were enrolled and dosed according to age and weight. Patients ≥6 to <12 years weighing <30 kg at baseline (n=31) were administered ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h. Patients ≥6 to <12 years weighing ≥30 kg at baseline were administered ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Patients ≥12 years at baseline were administered ELX 200 mg qd/TEZ 100 mg qd/IVA 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%).

Patients in these studies 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 medicinal products. Patients had a confirmed diagnosis of CF.

Study CFD-016 was an observational, retrospective study evaluating Real-World clinical outcomes in patients aged 6 years and older. Patients had at least one IVA/TEZ/ELX-responsive mutation and did not have an *F508del* mutation. A total of 422 patients were evaluated with a total of 82 IVA/TEZ/ELX-responsive non-*F508del* mutations represented. The mean $ppFEV_1$ at baseline was 74.15%.

In studies 445-102, 445-103, 445-104, 445-106, 445-111, and 445-124 patients continued their CF therapies, but discontinued any previous CFTR modulator therapies, except for study medicinal products. Patients 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 × ULN, or total bilirubin ≥2 × ULN), were excluded. In study 445-111, patients who had ALT or AST ≥2 × 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, 445-116, 445-111, and 445-124 were eligible to roll over into separate open-label extension studies.

Study 445-102

In study 445-102 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through week 24. Treatment with IVA/TEZ/ELX in combination with IVA 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 7). Mean improvement in $ppFEV_1$ was observed at the first assessment on day 15 and sustained through the 24-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region.

A total of 18 patients receiving IVA/TEZ/ELX in combination with IVA had $ppFEV_1$ <40 percentage points at baseline. The safety and efficacy in this subgroup were consistent to those observed in the overall

population. The mean treatment difference of IVA/TEZ/ELX in combination with IVA- compared to placebo-treated patients for absolute change in $ppFEV_1$ through week 24 in this subgroup was 18.4 percentage points (95% CI: 11.5, 25.3).

See Table 7 for a summary of primary and key secondary outcomes.

Table 7: Primary and key secondary efficacy analyses, full analysis set (study 445-102)

Analysis	Statistic	Placebo N=203	IVA/TEZ/ELX in combination with IVA N=200
Primary			
Baseline $ppFEV_1$	Mean (SD)	61.3 (15.5)	61.6 (15.0)
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
Baseline sweat chloride (mmol/L)	Mean (SD)	102.9 (9.8)	102.3 (11.9)
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 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)
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	70.0 (17.8)	68.3 (16.9)
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 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)
Baseline BMI (kg/m^2)	Mean (SD)	21.31 (3.14)	21.49 (3.07)
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)

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SD: Standard Deviation; 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.

Study 445-103
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 IVA/TEZ/ELX in combination with IVA compared to TEZ/IVA in combination with IVA 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 8). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region.

See Table 8 for a summary of primary and key secondary outcomes in the overall trial population.

In a post-hoc analysis of patients with (N=66) and without (N=41) recent CFTR modulator use, an improvement in $ppFEV_1$ of 7.8 percentage points (95% CI: 4.8, 10.8) and 13.2 percentage points (95% CI: 8.5, 17.9), respectively was observed.

Table 8: Primary and key secondary efficacy analyses, full analysis set (study 445-103)

Analysis*	Statistic	TEZ/IVA in combination with IVA N=52	IVA/TEZ/ELX in combination with IVA N=55
Primary			
Baseline $ppFEV_1$	Mean (SD)	60.2 (14.4)	61.6 (15.4)
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			
Baseline sweat chloride (mmol/L)	Mean (SD)	90.0 (12.3)	91.4 (11.0)
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)
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	72.6 (17.9)	70.6 (16.2)
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; SD: Standard Deviation; 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 TEZ/IVA in combination with IVA.

Study 445-104
In study 445-104 the primary endpoint was within-group mean absolute change in $ppFEV_1$ from baseline through week 8 for the IVA/TEZ/ELX in combination with IVA group. Treatment with IVA/TEZ/ELX in combination with IVA resulted in statistically significant improvement in $ppFEV_1$ from baseline of 3.7 percentage points (95% CI: 2.8, 4.6; $P < 0.0001$) (see Table 9). Overall improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, geographic region, and genotype groups (F/Gating or F/RF).

See Table 9 for a summary of primary and secondary outcomes in the overall trial population.

In a subgroup analysis of patients with an F/Gating genotype, the treatment difference of IVA/TEZ/ELX in combination with IVA (N=50) compared with IVA (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 IVA/TEZ/ELX in combination with IVA (N=82) compared with TEZ/IVA in combination with IVA (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/Gating and the F/RF genotype subgroups for improvement in sweat chloride and CFQ-R respiratory domain score were consistent with the overall results.

Table 9: Primary and secondary efficacy analyses, full analysis set (study 445-104)

Analysis*	Statistic	Control group† N=126	IVA/TEZ/ELX in combination with IVA N=132
Primary			
Baseline $ppFEV_1$	Mean (SD)	68.1 (16.4)	67.1 (15.7)
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 $ppFEV_1$ 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
Baseline sweat chloride (mmol/L)	Mean (SD)	56.4 (25.5)	59.5 (27.0)
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 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
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	77.3 (15.8)	76.5 (16.6)
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 (points) compared to the control group	Treatment difference (95% CI)	NA	8.7 (5.3, 12.1)

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SD: Standard Deviation; 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 IVA or TEZ/IVA in combination with IVA.

† IVA group or TEZ/IVA in combination with IVA group.

Study 445-105

Study 445-105 was a 192-week open-label extension study to evaluate the safety and efficacy of long-term treatment with IVA/TEZ/ELX in combination with IVA. Patients who rolled over from studies 445-102 (N=399) and 445-103 (N=107) received IVA/TEZ/ELX in combination with IVA.

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 IVA/TEZ/ELX in combination with IVA in the parent studies. Patients from the control arms as well as patients who received IVA/TEZ/ELX in combination with IVA in the parent studies, showed sustained improvements. Secondary efficacy endpoints are summarised in Table 10.

Table 10: Study 445-105 secondary efficacy analysis, full analysis set (F/MF and F/F subjects)

		Study 445-105 week 192			
Analysis	**Statistic**	**Placebo in 445-102 N=203**	**IVA/TEZ/ELX in 445-102 N=196**	**TEZ/IVA in 445-103 N=52**	**IVA/TEZ/ELX in 445-103 N=55**
Absolute change from baseline* in $ppFEV_1$ (percentage points)	n **LS mean** 95% CI	136 **15.3** (13.7, 16.8)	133 **13.8** (12.3, 15.4)	32 **10.9** (8.2, 13.6)	36 **10.7** (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 Triple Combination (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 RD 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; 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; n = size of subsample

* Baseline = parent study baseline

† For subjects who were randomised to the IVA/TEZ/ELX 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 study 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 445-124

The safety and efficacy of IVA/TEZ/ELX in 307 patients with CF aged 6 years and older without an *F508del* mutation but with a qualifying IVA/TEZ/ELX-responsive *CFTR* mutation were evaluated (study 445-124).

In study 445-124 the primary endpoint of efficacy was mean absolute change in $ppFEV_1$ from baseline through week 24. Secondary endpoints were absolute change in sweat chloride, CFQ-R respiratory domain

score, growth parameters (BMI, weight), and number of PEx. See Table 11 for a summary of primary and secondary efficacy outcomes.

Table 11: Primary and secondary efficacy analyses, full analysis set (study 445-124)			
Analysis	**Statistic**	**Placebo N=102**	**IVA/TEZ/ELX 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)
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; CI: Confidence Interval; IV: intravenous; IVA: ivacaftor; LS: Least Squares;; N: total sample size; *P*: probability; PEx: Pulmonary Exacerbation; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; SE: Standard Error; SwCl: Sweat Chloride; TEZ: tezacaftor			

Study CFD-016
Study CFD-016 included 422 homozygotic non-*F508del* CF patients harbouring at least one IVA/TEZ/ELX-responsive *CFTR* mutation based on *in vitro* FRT data. After a median follow-up of 1.31 year, the mean change in $ppFEV_1$ was 4.53% (95% CI: 3.5, 5.56). Almost all subgroups according to *CFTR* mutation that included ≥5 patients showed an improvement in $ppFEV_1$ over that time, except for the subgroup with R74W.

Paediatric population

Paediatric patients aged 2 to <12 years

Study 445-106
In study 445-106, the primary endpoint of safety and tolerability was evaluated through 24 weeks in patients aged 6 to less than 12 years. Secondary endpoints were evaluation of pharmacokinetics and efficacy.

See Table 12 for a summary of secondary efficacy outcomes.

Table 12: Secondary efficacy analyses, full analysis set (N=66) (study 445-106)			
Analysis	**Baseline Mean (SD)**	**Absolute change through week 12 Within-group change (95% CI)**	**Absolute change through week 24 Within-group change (95% CI)***
$ppFEV_1$ (percentage points)	n=62 88.8 (17.7)	n=59 9.6 (7.3, 11.9)	n=59 10.2 (7.9, 12.6)
CFQ-R respiratory domain score (points)	n=65 80.3 (15.2)	n=65 5.6 (2.9, 8.2)	n=65 7.0 (4.7, 9.2)
BMI-for-age z-score	n=66 -0.16 (0.74)	n=58 0.22 (0.13, 0.30) †	n=33 0.37 (0.26, 0.48) ‡
Weight-for-age z-score	n=66 -0.22 (0.76)	n=58 0.13 (0.07, 0.18) †	n=33 0.25 (0.16, 0.33) ‡
Height-for-age z-score	n=66 -0.11 (0.98)	n=58 -0.03 (-0.06, 0.00) †	n=33 -0.05 (-0.12, 0.01) ‡
Number of pulmonary exacerbations††	N/A	N/A	n=66 4 (0.12) §
$LCI_{2.5}$	n=53 9.77 (2.68)	n=48 -1.83 (-2.18, -1.49)	n=50 -1.71 (-2.11, -1.30)

SD: Standard Deviation; CI: Confidence Interval; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: Body Mass Index; N/A: Not Applicable; LCI: Lung Clearance Index; n: size of subsample

* Not all participants included in the analyses had data available for all follow-up visits, especially from week 16 onwards. The ability to collect data at week 24 was hampered by the COVID-19 pandemic. Week 12 data were less impacted by the pandemic.

† At week 12 assessment.

‡ At week 24 assessment.

†† 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

Study 445-107 is 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 IVA/TEZ/ELX in patients who completed study 445-106. Efficacy endpoints were included as secondary endpoints. The final analysis of this study was conducted in 64 paediatric patients aged 6 years and older. With 192 additional weeks of treatment, sustained improvements in $ppFEV_1$, SwCl, CFQ-R RD score, and $LCI_{2.5}$ were shown, consistent with the results observed in the study 445-106.

Study 445-116

In study 445-116 treatment with IVA/TEZ/ELX in combination with IVA in patients aged 6 to less than 12 years resulted in statistically significant improvement through 24 weeks in the primary endpoint ($LCI_{2.5}$). The LS mean treatment difference for the IVA/TEZ/ELX in combination with IVA group versus placebo for the absolute change in $LCI_{2.5}$ from baseline through week 24 was -2.26 (95% CI: -2.71, -1.81; $P < 0.0001$).

Study 445-111

In study 445-111 the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints included an evaluation of pharmacokinetics, and efficacy endpoints including

absolute change in sweat chloride (see Pharmacodynamic effects) and $LCI_{2.5}$ from baseline through week 24. See Table 13 for a summary of secondary efficacy outcomes.

Table 13: Secondary efficacy analyses, full analysis set (study 445-111)	
Analysis	**Within-group change (95% CI) for IVA/TEZ/ELX in combination with IVA**
Absolute change in sweat chloride from baseline through week 24 (mmol/L)	N=75 -57.9 (-61.3, -54.6)
Absolute change in $LCI_{2.5}$ from baseline through week 24	N=63* -0.83 (-1.01, -0.66)
CI: Confidence Interval; LCI: Lung Clearance Index * LCI assessed only on patients aged 3 years and older at screening.	

Study 445-124
In study 445-124, the safety and efficacy of IVA/TEZ/ELX in patients with CF aged 6 years and older without an *F508del* mutation were evaluated. A post-hoc efficacy analysis was conducted in 31 patients aged 6-12 years, of whom 23 patients received IVA/TEZ/ELX. The mean change (SD) from baseline was 10.2% (16.2) for $ppFEV_1$ and -37.7 (18.8) mmol/L for sweat chloride.

The European Medicines Agency has deferred the obligation to submit the results of studies with IVA/TEZ/ELX in combination with IVA in one or more subset of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ELX, TEZ and IVA are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of ELX and TEZ and twice-daily dosing of IVA, plasma concentrations of ELX, TEZ and IVA reach steady state within approximately 7 days for ELX, within 8 days for TEZ, and within 3-5 days for IVA. Upon dosing IVA/TEZ/ELX to steady state, the accumulation ratio is approximately 3.6 for ELX, 2.8 for TEZ and 4.7 for IVA. Key pharmacokinetic parameters for ELX, TEZ and IVA at steady state in patients with CF aged 12 years and older are shown in Table 14.

Table 14: Mean (SD) pharmacokinetic parameters of ELX, TEZ and IVA at steady state in patients with CF aged 12 years and older			
Dose	**Active Substance**	**C_{max} (µg/mL)**	**$AUC_{0\text{-}24h,\ ss}$ or $AUC_{0\text{-}12h,ss}$ (µg·h/mL)***
IVA 150 mg every 12 hours/TEZ 100 mg and ELX 200 mg once daily	ELX	9.15 (2.09)	162 (47.5)
	TEZ	7.67 (1.68)	89.3 (23.2)
	IVA	1.24 (0.34)	11.7 (4.01)
SD: Standard Deviation; C_{max}: maximum observed concentration; AUC_{ss}: Area Under the Concentration versus time curve at steady state * $AUC_{0\text{-}24h}$ for ELX and TEZ and $AUC_{0\text{-}12h}$ for IVA.			

Absorption

The absolute bioavailability of ELX when administered orally in the fed state is approximately 80%. ELX 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 TEZ and IVA is approximately 3 hours (2 to 4 hours) and 4 hours (3 to 6 hours), respectively. ELX exposure (AUC) increases approximately 1.9- to 2.5-fold when

administered with a moderate-fat meal relative to fasted conditions. IVA 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 TEZ (see section 4.2).

As exposures of ELX were approximately 20% lower after administration of the IVA/TEZ/ELX granules relative to the reference IVA/TEZ/ELX tablet, the formulations are not considered interchangeable.

Distribution

ELX is >99% bound to plasma proteins and TEZ is approximately 99% bound to plasma proteins, in both cases primarily to albumin. IVA 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 IVA/TEZ/ELX in combination with IVA, the mean (±SD) apparent volume of distribution of ELX, TEZ and IVA was 53.7 L (17.7), 82.0 L (22.3) and 293 L (89.8), respectively. ELX, TEZ and IVA do not partition preferentially into human red blood cells.

Biotransformation

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

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

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

The effect of the CYP3A4*22 heterozygous genotype on TEZ, IVA and ELX exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. No dose-adjustment of TEZ, IVA or ELX is considered necessary. The effect in CYP3A4*22 homozygous genotype patients is expected to be stronger. However, no data are available for such patients.

Elimination

Following multiple dosing in the fed state, the mean (±SD) apparent clearance values of ELX, TEZ and IVA 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 ELX, TEZ and IVA following administration of the IVA/TEZ/ELX 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-life of TEZ following administration of the IVA/TEZ/ELX fixed-dose combination tablets is 11.9 (3.79) hours.

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

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

For ELX, TEZ and IVA there was negligible urinary excretion of unchanged medicine.

Hepatic impairment

ELX alone or in combination with TEZ and IVA has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of ELX, TEZ and IVA for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had an approximately 25% higher AUC and a 12% higher C_{max} for ELX, 73% higher AUC and a 70% higher C_{max} for M23-ELX, 20% higher AUC but similar C_{max} for TEZ, 22% lower AUC and a 20% lower C_{max} for M1-TEZ, and a 1.5-fold higher AUC and a 10% higher C_{max} for IVA compared with healthy subjects matched for demographics. The effect of moderately impaired hepatic function on total exposure (based on summed values of ELX and its M23-ELX metabolite) was 36% higher AUC and a 24% higher C_{max} compared with healthy subjects matched for demographics (see sections 4.2, 4.4, and 4.8).

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

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

Renal impairment

ELX alone or in combination with TEZ and IVA has not been studied in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) less than 30 mL/min] or in patients with end-stage renal disease.

In human pharmacokinetic studies of ELX, TEZ and IVA, there was minimal elimination of ELX, TEZ and IVA in urine (only 0.23%, 13.7% [0.79% as unchanged medicine] and 6.6% of total radioactivity, respectively).

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

In population PK analysis conducted in 817 patients administered TEZ alone or in combination with IVA in phase 2 or phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min) did not affect the clearance of TEZ significantly (see sections 4.2 and 4.4).

Gender

The pharmacokinetic parameters of ELX (244 males compared to 174 females), TEZ and IVA are similar in males and females.

Race

Race had no clinically meaningful effect on ELX exposure based on population PK analysis in whites (N=373) and non-whites (N=45). The non-white races consisted of 30 Blacks or African Americans, 1 with multiple racial background and 14 with other ethnic background (no Asians).

Very limited PK data indicate comparable exposure of TEZ in whites (N=652) and non-whites (N=8). The non-white races consisted of 5 Blacks or African Americans and 3 Native Hawaiians or other Pacific Islanders.

Race had no clinically meaningful effect on the PK of IVA in whites (N=379) and non-whites (N=29) based on a population PK analysis. The non-white races consisted of 27 African Americans and 2 Asians.

Elderly

Clinical trials of IVA/TEZ/ELX in combination with IVA did not include sufficient number of patients aged 65 years and older to determine whether response in these patients is different from younger adults (see section 4.4).

Paediatric population

ELX, TEZ and IVA exposures observed in phase 3 studies as determined using population PK analysis are presented by age group in Table 15. Exposures of ELX, TEZ and IVA in patients aged 2 to less than 18 years are within the range observed in patients aged 18 years and older.

Table 15: Mean (SD) ELX, M23-ELX, TEZ, M1-TEZ and IVA exposures observed at steady state by age group and dose administered						
Age/Weight group	**Dose**	**ELX $AUC_{0\text{-}24h,\ ss}$ (µg·h/mL)**	**M23-ELX $AUC_{0\text{-}24h,\ ss}$ (µg·h/mL)**	**TEZ $AUC_{0\text{-}24h,\ ss}$ (µg·h/mL)**	**M1-TEZ $AUC_{0\text{-}24h,\ ss}$ (µg·h/mL)**	**IVA $AUC_{0\text{-}12h,\ ss}$ (µg·h/mL)**
Patients aged 2 to <6 years, 10 kg to <14 kg (N=16)	IVA 60 mg qAM/ TEZ 40 mg qd/ ELX 80 mg qd and IVA 59.5 mg qPM	128 (24.8)	56.5 (29.4)	87.3 (17.3)	194 (24.8)	11.9 (3.86)
Patients aged 2 to <6 years, ≥14 kg (N=59)	IVA 75 mg q12h/ TEZ 50 mg qd/ ELX 100 mg qd	138 (47.0)	59.0 (32.7)	90.2 (27.9)	197 (43.2)	13.0 (6.11)
Patients aged 6 to <12 years, <30 kg (N=36)	IVA 75 mg q12h/ TEZ 50 mg qd/ ELX 100 mg qd	116 (39.4)	45.4 (25.2)	67.0 (22.3)	153 (36.5)	9.78 (4.50)
Patients aged 6 to <12 years, ≥30 kg (N=30)	IVA 150 mg q12h/TEZ 100 mg qd/ ELX 200 mg qd	195 (59.4)	104 (52.0)	103 (23.7)	220 (37.5)	17.5 (4.97)
Adolescent patients (12 to <18 years) (N=72)	IVA 150 mg q12h/ TEZ 100 mg qd/ ELX 200 mg qd	147 (36.8)	58.5 (25.6)	88.8 (21.8)	148 (33.3)	10.6 (3.35)
Adult patients (≥18 years) (N=179)	IVA 150 mg q12h/ TEZ 100 mg qd/ ELX 200 mg qd	168 (49.9)	64.6 (28.9)	89.5 (23.7)	128 (33.7)	12.1 (4.17)
SD: Standard Deviation; AUC_{ss}: Area Under the Concentration versus time curve at steady state; qd: once daily; qAM: once each morning; qPM: once each evening; q12h: once every 12 hours						

5.3 Preclinical safety data

Elexacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility and pregnancy
The No Observed Adverse Effect Level (NOAEL) for fertility findings was 55 mg/kg/day (2 times the maximum recommended human dose (MRHD) based on summed AUCs of ELX and its metabolite) in male rats and 25 mg/kg/day (4 times the MRHD based on summed AUCs of ELX and its metabolite) in female rats. In rat, at doses exceeding the maximum tolerated dose (MTD), degeneration and atrophy of seminiferous tubules are correlated to oligo-/aspermia and cellular debris in epididymides. In dog testes, minimal or mild, bilateral degeneration/atrophy of the seminiferous tubules was present in males administered 14 mg/kg/day ELX (15 times the MRHD based on summed AUCs of ELX and its metabolite) that did not resolve during the recovery period, however without further sequelae. The human relevance of these findings is unknown.

ELX was not teratogenic in rats at 40 mg/kg/day and at 125 mg/kg/day in rabbits (approximately 9 and 4 times, respectively, the MRHD based on summed AUCs of ELX and its metabolite [for rat] and AUC of ELX [for rabbit]) with developmental findings being limited to lower mean foetal body weight at ≥25 mg/kg/day.

Placental transfer of ELX was observed in pregnant rats.

Tezacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Placental transfer of TEZ was observed in pregnant rats.

Juvenile toxicity studies in rats exposed during postnatal day 7 to 35 (PND 7-35) showed mortality and moribundity, even at low doses. Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period. Exposure in rats from PND 21-49 did not show toxicity at the highest dose which was approximately two times the intended human exposure. Tezacaftor and its metabolite, M1-TEZ, are substrates for P-glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are likely not relevant for the indicated paediatric population of 2 years of age and older, for whom P-glycoprotein expression levels are equivalent to levels observed in adults.

Ivacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility and pregnancy
The NOAEL for fertility findings was 100 mg/kg/day (5 times the MRHD based on summed AUCs of IVA and its metabolites) in male rats and 100 mg/kg/day (3 times the MRHD based on summed AUCs of IVA and its metabolites) in female rats.

In the pre- and post-natal study IVA decreased survival and lactation indices and caused a reduction in pup body weights. The NOAEL for viability and growth in the offspring provides an exposure level of approximately 3 times the systemic exposure of IVA and its metabolites in adult humans at the MRHD. Placental transfer of IVA was observed in pregnant rats and rabbits.

Juvenile animal studies
Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through day 35 at IVA exposure levels of 0.21 time the MRHD based on systemic exposure of IVA and its metabolites. This finding has not been observed in foetuses derived from rat dams treated with IVA on gestation days 7 to day 17, in rat pups exposed to IVA through milk ingestion up to postnatal day 20, in 7-week-old rats, nor in 3.5- to 5-month-old dogs treated with IVA. The potential relevance of these findings in humans is unknown (see section 4.4).

Ivacaftor/tezacaftor/elexacaftor

Combination repeat-dose toxicity studies in rats and dogs involving the co-administration of ELX, TEZ and IVA to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions. The potential for synergistic toxicity on male reproduction has not been assessed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous (E551)
Croscarmellose sodium (E468)
Hypromellose (E464)
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate (E470b)
Mannitol (E421)
Sodium laurilsulfate (E487)
Sucralose (E955)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once mixed, the mixture has been shown to be stable for one hour.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Pack size of 28 sachets (4 weekly wallets, each with 7 sachets).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/003
EU/1/20/1468/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 August 2020
Date of latest renewal: 22 May 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post Authorisation Efficacy Study (PAES): In order to further characterise the long-term efficacy among children with CF who are heterozygous for *F508del* and aged 2 through 5 years, the MAH should conduct and submit the results of a long-term effectiveness registry-based study comparing disease progression among children with CF who are heterozygous for F508del-CFTR and are aged 2 through 5 years at the time of Kaftrio treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kaftrio treatment, in addition to a longitudinal historical cohort, according to an agreed protocol.	Full protocol submission by June 2024 Enrolment completed by Dec 2024 Final report Due date 31 Dec 2029

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 37.5 mg of ivacaftor, 25 mg of tezacaftor and 50 mg of elexacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take the tablets with fat-containing food.

You may start taking Kaftrio on any day of the week.

Open

Insert tab below to close

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kaftrio 37.5 mg/25 mg/50 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 37.5 mg of ivacaftor, 25 mg of tezacaftor and 50 mg of elexacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take the tablets with fat-containing food.

You may start taking Kaftrio on any day of the week.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 37.5 mg/25 mg/50 mg tablets
ivacaftor/tezacaftor/elexacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take the tablets with fat-containing food.

You may start taking Kaftrio on any day of the week.

Open

Insert tab below to close

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kaftrio 75 mg/50 mg/100 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take the tablets with fat-containing food.

You may start taking Kaftrio on any day of the week.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg tablets
ivacaftor/tezacaftor/elexacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg granules in sachet
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 75 mg of ivacaftor, 50 mg of tezacaftor, and 100 mg of elexacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

28 sachets

4 individual wallets with 7 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Before consuming entire mixture, look inside the sachet to make sure there are no granules left inside.

Use within one hour after mixing, just before or after a fat-containing meal or snack.

Lift here to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kaftrio 75 mg/50 mg/100 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg granules in sachet
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 75 mg of ivacaftor, 50 mg of tezacaftor, and 100 mg of elexacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

7 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Before consuming entire mixture, look inside the sachet to make sure there are no granules left inside.

Use within one hour after mixing, just before or after a fat-containing meal or snack.

Use all 7 days' doses before starting a new wallet.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/004

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kaftrio 75 mg/50 mg/100 mg granules
ivacaftor/tezacaftor/elexacaftor
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Vertex Pharmaceuticals

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 60 mg/40 mg/80 mg granules in sachet
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 60 mg of ivacaftor, 40 mg of tezacaftor, and 80 mg of elexacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

28 sachets

4 individual wallets with 7 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Before consuming entire mixture, look inside the sachet to make sure there are no granules left inside.

Use within one hour after mixing, just before or after a fat-containing meal or snack.

Lift here to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kaftrio 60 mg/40 mg/80 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 60 mg/40 mg/80 mg granules in sachet
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 60 mg of ivacaftor, 40 mg of tezacaftor, and 80 mg of elexacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

7 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Before consuming entire mixture, look inside the sachet to make sure there are no granules left inside.

Use within one hour after mixing, just before or after a fat-containing meal or snack.

Use all 7 days' doses before starting a new wallet.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
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12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kaftrio 60 mg/40 mg/80 mg granules
ivacaftor/tezacaftor/elexacaftor
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Vertex Pharmaceuticals

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kaftrio is and what it is used for

Kaftrio contains three active substances: ivacaftor, tezacaftor and elexacaftor. The medicine helps lung cells to work better in some patients with cystic fibrosis (CF). CF is an inherited condition in which the lungs and the digestive system can become clogged with thick, sticky mucus.

Kaftrio taken with ivacaftor is for **patients aged 6 years and over who have CF, with at least one mutation** in the *CFTR* (*cystic fibrosis transmembrane conductance regulator*) gene that is responsive to Kaftrio. It is intended as a long-term treatment.

Kaftrio works on a protein called CFTR. The protein is damaged in some people with CF, if they have a mutation in the *CFTR* gene.

Kaftrio is normally taken with another medicine, ivacaftor. Ivacaftor causes the protein to work better, while tezacaftor and elexacaftor increase the amount of protein at the cell surface.

Kaftrio (taken with ivacaftor) helps your breathing by improving your lung function. You may also notice that you do not get ill as often, or that it is easier to gain weight.

2. What you need to know before you take Kaftrio

Do not take Kaftrio:
- **If you are allergic** to ivacaftor, tezacaftor, elexacaftor, or any other ingredients of this medicine (listed in section 6).
- **Talk to your doctor** and do not take the tablets, if this applies to you.

Warnings and precautions

Talk to your doctor if you have liver problems or have had them previously. Your doctor may need to adjust your dose (see section 4).

- Your doctor will do some **blood tests to check your liver** before and during treatment with Kaftrio, especially if your blood tests showed high liver enzymes in the past. Liver enzymes in the blood can increase in patients receiving Kaftrio.

Tell your doctor right away if you have any symptoms of liver problems. These are listed in section 4.

- Depression (including suicidal thoughts, changes in behaviours, anxiety, and sleep disorders) has been reported in patients while taking Kaftrio, usually starting within the first three months of treatment. **Talk to your doctor straight away if you (or someone taking this medicine) experience any of the following symptoms which may be signs of depression:** sad or altered mood, anxiety, feelings of emotional discomfort or thoughts of harming or killing yourself, and/or sleep difficulties (see section 4).

  Talk to your doctor if you recognize behavioural changes in your child within the first 2 months of treatment initiation.

- **Talk to your doctor if you have kidney problems,** or you have previously had them.

- **If you have two Class I mutations** (mutations known not to make CFTR protein), you should not take Kaftrio, as you are not expected to respond to this medicine.

- **Talk to your doctor** before starting treatment with Kaftrio if you have received **an organ transplant**.

- **Talk to your doctor** if you are using hormonal contraception – for example, women using the contraceptive pill. This may mean you are more likely to get a rash while taking Kaftrio.

- **Your doctor may do eye examinations** before and during treatment with Kaftrio. Cloudiness of the eye lens (cataract) without any effect on vision has occurred in some children and adolescents receiving this treatment.

Children under 6 years
Do not give this medicine to children under the age of 6 years because it is not known if Kaftrio tablets are safe and effective in this age group.

Other medicines and Kaftrio
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Some medicines can affect how Kaftrio works or may make side effects more likely. In particular, tell your doctor if you take any of the medicines listed below. Your doctor may change the dose of one of the medicines if you take any of these.
- **Antifungal medicines** (used for the treatment of fungal infections). These include fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole.
- **Antibiotic medicines** (used for the treatment of bacterial infections). These include clarithromycin, erythromycin, rifampicin, rifabutin and telithromycin.
- **Epilepsy medicines** (used for the treatment of epileptic seizures or fits). These include carbamazepine, phenobarbital and phenytoin.

- **Herbal medicines.** These include St. John's wort (*Hypericum perforatum*).
- **Immunosuppressants** (used after an organ transplantation). These include ciclosporin, everolimus, sirolimus and tacrolimus.
- **Cardiac glycosides** (used for the treatment of some heart conditions). These include digoxin.
- **Anticoagulant medicines** (used to prevent blood clots). These include warfarin.
- **Medicines for diabetes.** These include glimepiride, glipizide, glyburide, nateglinide and repaglinide.
- **Medicines for lowering blood cholesterol.** These include pitavastatin and rosuvastatin.
- **Medicines for lowering blood pressure.** These include verapamil.

Kaftrio with food and drink
Avoid food or drinks containing grapefruit during treatment as these may increase the side effects of Kaftrio by increasing the amount of Kaftrio in your body.

Pregnancy and breast-feeding
- **Ask your doctor for advice** before taking this medicine if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.
  - **Pregnancy:** It may be better to avoid using this medicine during pregnancy. Your doctor will help you decide what is best for you and your child.
  - **Breast-feeding:** Ivacaftor, tezacaftor, and elexacaftor have been detected in breastfed babies. Your doctor will consider the benefit of breast-feeding for your baby and the benefit of treatment for you to help you decide whether to stop breast-feeding or to stop treatment.

Driving and using machines
Kaftrio can make you dizzy. If you feel dizzy, do not drive, cycle, or use machines unless you are not affected.

Kaftrio contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

3. How to take Kaftrio

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will determine the correct dose for you.

Kaftrio is usually taken with ivacaftor.

Recommended dose for patients aged 6 years and over

Age	Weight	Morning dose	Evening dose
6 to < 12 years	< 30 kg	Two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets	One ivacaftor 75 mg tablet
6 to < 12 years	≥ 30 kg	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet
12 years and older	-	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet

Take the morning and evening tablets about 12 hours apart.

The tablets are for oral use.

Take both Kaftrio and ivacaftor tablets with food that contains fat. Meals or snacks that contain fat include those prepared with butter or oils or those containing eggs. Other fat-containing foods are:
- Cheese, whole milk, whole milk dairy products, yogurt, chocolate
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

Avoid food and drink containing grapefruit while you are taking Kaftrio. See *Kaftrio with food and drink* in section 2 for more details.

Swallow the tablets whole. Do not chew, crush or break the tablets before swallowing.

You must keep using all your other medicines, unless your doctor tells you to stop.

If you have liver problems, either moderate or severe, your doctor may reduce the dose of your tablets or decide to stop treatment with Kaftrio. See also *Warnings and precautions* in section 2.

If you take more Kaftrio than you should
Contact your doctor or pharmacist for advice. If possible, take your medicine and this leaflet with you. You may get side effects, including those mentioned in section 4 below.

If you forget to take Kaftrio
If you forget a dose, work out how long it is since the dose you missed.
- **If less than 6 hours** have passed since you missed a dose, either morning or evening, take the forgotten tablet(s) as soon as possible. Then go back to your usual schedule.
- **If more than 6 hours** have passed:
  - **If you missed a morning dose** of Kaftrio, take it as soon as you remember. Do not take the evening dose of ivacaftor. Take the next morning dose at the usual time.
  - **If you missed an evening** dose of ivacaftor, do not take the missed dose. Wait for the next day and take the morning dose of Kaftrio tablets as usual.

Do not take a double dose to make up for any missed tablets.

If you stop taking Kaftrio
Your doctor will tell you how long you need to keep taking Kaftrio. It is important to take this medicine regularly. Do not make changes unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects:

Possible signs of liver problems
Liver damage and worsening of liver function in people with or without liver disease. The worsening of liver function can be serious and may require transplantation (see section 2).

Increased liver enzymes in the blood are very common in patients treated with Kaftrio. These may be signs of liver problems:
- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Depression. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort (see section 2).

Tell your doctor straight away if you have any of these symptoms.

Very common side effects (may affect more than 1 in 10 people)
- Rash (more common in children, and in women compared to men)

Tell your doctor straight away if you notice a rash.

Other side effects:
Very common (may affect more than 1 in 10 people)
- Headache
- Dizziness
- Upper respiratory tract infection (common cold)
- Oropharyngeal pain (sore throat)
- Nasal congestion
- Stomach or abdominal pain
- Diarrhoea
- Increased liver enzymes (signs of stress on the liver)
- Changes in the type of bacteria in mucus
- Increased creatine phosphokinase (sign of muscle breakdown) seen in blood tests

Common (may affect up to 1 in 10 people)
- Flu
- Abnormal breathing (shortness of breath or difficulty breathing)
- Low blood sugar (hypoglycaemia)
- Runny nose
- Sinus problems (sinus congestion)
- Redness or soreness in the throat
- Ear problems: ear pain or discomfort, ringing in the ears, inflamed eardrum
- Spinning sensation (inner ear disorder)
- Wind (flatulence)
- Spots (acne)
- Itchy skin
- Breast mass
- Feeling nauseous

Uncommon (may affect up to 1 in 100 people)
- Breast and nipple problems: inflammation, pain
- Enlargement of the breast in men
- Increases in blood pressure
- Wheezing
- Blocked ears (ear congestion)

Not known (frequency cannot be estimated from the available data)
- Allergic reactions (hypersensitivity)
- Damage to the liver (liver injury)
- Raised bilirubin measurement (liver blood test)
- Behavioural changes

Additional side effects in adolescents
Side effects in adolescents are similar to those observed in adults.

Additional side effects in children
Most cases of behavioural changes have been reported in younger children aged 2-5 years.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kaftrio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Kaftrio contains
- The active substances are ivacaftor, tezacaftor and elexacaftor.

Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets
Each film-coated tablet contains 37.5 mg of ivacaftor, 25 mg of tezacaftor and 50 mg of elexacaftor.

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
Each film-coated tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

- The other ingredients are:
  - Tablet core: Hypromellose (E464), hypromellose acetate succinate, sodium laurilsulfate (E487), croscarmellose sodium (E468), microcrystalline cellulose (E460(i)), and magnesium stearate (E470b).
  - Tablet film coating: Hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), and iron oxide red (E172).

See the end of section 2 for important information about the contents of Kaftrio.

What Kaftrio looks like and contents of the pack
Kaftrio 37.5 mg/25 mg/50 mg film-coated tablets are light orange, capsule-shaped tablets stamped with "T50" on one side and plain on the other.

Kaftrio 75 mg/50 mg/100 mg film-coated tablets are orange, capsule-shaped tablets stamped with "T100" on one side and plain on the other.

Kaftrio is available in pack size of 56 tablets (4 blister cards, each with 14 tablets).

Marketing Authorisation Holder
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Almac Pharma Services (Ireland) Limited
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the patient

Kaftrio 60 mg/40 mg/80 mg granules in sachet
Kaftrio 75 mg/50 mg/100 mg granules in sachet
ivacaftor/tezacaftor/elexacaftor

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child.
- If you get any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kaftrio is and what it is used for

Kaftrio contains three active substances: ivacaftor, tezacaftor and elexacaftor. The medicine helps lung cells to work better in some patients with cystic fibrosis (CF). CF is an inherited condition in which the lungs and the digestive system can become clogged with thick, sticky mucus.

Kaftrio taken with ivacaftor is for **patients aged 2 to less than 6 years who have CF, with at least one mutation** in the *CFTR* (*cystic fibrosis transmembrane conductance regulator*) gene that is responsive to Kaftrio. It is intended as a long-term treatment.

Kaftrio works on a protein called CFTR. The protein is damaged in some people with CF, if they have a mutation in the *CFTR* gene.

Kaftrio is normally taken with another medicine, ivacaftor. Ivacaftor causes the protein to work better, while tezacaftor and elexacaftor increase the amount of protein at the cell surface.

Kaftrio (taken with ivacaftor) helps your child's breathing by improving his/her lung function. You may also notice that your child does not get ill as often, or that it is easier for your child to gain weight.

2. What you need to know before your child takes Kaftrio

Do not give your child Kaftrio:
- **If your child is allergic** to ivacaftor, tezacaftor, elexacaftor, or any other ingredients of this medicine (listed in section 6).
- **Talk to your child's doctor** and do not give your child this medicine, if this applies to your child.

Warnings and precautions

Talk to your child's doctor if your child has liver problems or have had them previously. Your doctor may need to adjust your child's dose (see section 4).

- Your doctor will do some **blood tests to check your child's liver** before and during treatment with Kaftrio, especially if your child's blood tests showed high liver enzymes in the past. Liver enzymes in the blood can increase in patients receiving Kaftrio.

Tell your doctor right away if your child has any symptoms of liver problems. These are listed in section 4.

- Depression (including suicidal thoughts, changes in behaviours, anxiety, and sleep disorders) has been reported in patients while taking Kaftrio, usually starting within the first three months of treatment. **Talk to your doctor straight away if you (or someone taking this medicine) experience any of the following symptoms which may be signs of depression:** sad or altered mood, anxiety, feelings of emotional discomfort or thoughts of harming or killing yourself, and/or sleep difficulties (see section 4).

  Talk to your doctor if you recognize behavioural changes in your child within the first 2 months of treatment initiation.

- **Talk to your child's doctor if your child has kidney problems,** or your child has previously had them.

- **If your child has two Class I mutations** (mutations known not to make CFTR protein) you should not give Kaftrio to your child, as they are not expected to respond to this medicine.

- **Talk to your child's doctor** before starting treatment with Kaftrio if your child has received **an organ transplant**.

- **Your child's doctor may do eye examinations** before and during treatment with Kaftrio. Cloudiness of the eye lens (cataract) without any effect on vision has occurred in some children and adolescents receiving this treatment.

Children under 2 years
Do not give Kaftrio granules to children under the age of 2 years because it is not known if Kaftrio granules are safe and effective in this age group.

Other medicines and Kaftrio
Tell your child's doctor or pharmacist if your child is taking, has recently taken, or might take any other medicines. Some medicines can affect how Kaftrio works or may make side effects more likely. In particular, tell your child's doctor if you take any of the medicines listed below. Your child's doctor may change the dose of one of the medicines if your child takes any of these.
- **Antifungal medicines** (used for the treatment of fungal infections). These include fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole.
- **Antibiotic medicines** (used for the treatment of bacterial infections). These include clarithromycin, erythromycin, rifampicin, rifabutin and telithromycin.
- **Epilepsy medicines** (used for the treatment of epileptic seizures or fits). These include carbamazepine, phenobarbital and phenytoin.
- **Herbal medicines.** These include St. John's wort (*Hypericum perforatum*).

- **Immunosuppressants** (used after an organ transplantation). These include ciclosporin, everolimus, sirolimus and tacrolimus.
- **Cardiac glycosides** (used for the treatment of some heart conditions). These include digoxin.
- **Anticoagulant medicines** (used to prevent blood clots). These include warfarin.
- **Medicines for diabetes.** These include glimepiride, glipizide, glyburide, nateglinide and repaglinide.
- **Medicines for lowering blood cholesterol.** These include pitavastatin and rosuvastatin.
- **Medicines for lowering blood pressure.** These include verapamil.

Kaftrio with food and drink
Avoid giving your child food or drinks containing grapefruit during treatment as these may increase the side effects of Kaftrio by increasing the amount of Kaftrio in your child's body.

Driving and using machines
Kaftrio can make your child dizzy. If your child feels dizzy, it is advised that your child does not ride his/her bike or do anything else that needs his/her full attention.

Kaftrio granules contains lactose and sodium
If you have been told by your child's doctor that your child has an intolerance to some sugars, contact your child's doctor before your child takes this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

3. How to take Kaftrio

Always give your child this medicine exactly as your child's doctor or pharmacist has told you. Check with your child's doctor or pharmacist if you are not sure.

Your child's doctor will determine the correct dose for your child. Your child must keep using all other medicines, unless your child's doctor tells him/her to stop using any.

Kaftrio is usually taken with ivacaftor.

Recommended dose for patients aged 2 to less than 6 years

Age	Weight	Morning dose	Evening dose
2 to less than 6 years	10 kg to < 14 kg	One sachet of ivacaftor 60 mg/tezacaftor 40 mg/elexacaftor 80 mg granules	One sachet of ivacaftor 59.5 mg granules
	≥ 14 kg	One sachet of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg granules	One sachet of ivacaftor 75 mg granules

Give your child the morning and evening doses about 12 hours apart.

The granules are for oral use.

To prepare Kaftrio granules:
- Hold the sachet with the cut line on top.
- Shake the sachet gently to settle the Kaftrio granules.
- Tear or cut sachet open along cut line.

- Carefully pour all the Kaftrio granules in the sachet into 1 teaspoon (5 mL) of soft food or liquid in a small container (like an empty bowl). Look inside the sachet to make sure there are no granules left inside.
    - The food or liquid should be at or below room temperature.
    - Examples of soft foods or liquids include pureed fruits, flavoured yogurt or pudding, and milk or juice.
- Mix the Kaftrio granules with food or liquid.

After mixing, give Kaftrio within 1 hour. Make sure all the medicine is taken.

Give both Kaftrio and ivacaftor doses with food that contains fat. Meals or snacks that contain fat include those prepared with butter or oils or those containing eggs. Other fat-containing foods are:

- Cheese, whole milk, whole milk dairy products, yogurt, chocolate
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

Avoid giving your child food and drink containing grapefruit while your child is taking Kaftrio. See *Kaftrio with food and drink* in section 2 for more details.

If your child has liver problems, either moderate or severe, your child's doctor may reduce the dose of your child's medicine or decide to stop treatment with Kaftrio. See also *Warnings and precautions* in section 2.

If your child takes more Kaftrio than he/she should
Contact your child's doctor or pharmacist for advice. If possible, take your child's medicine and this leaflet with you. Your child may get side effects, including those mentioned in section 4 below.

If you forget to give your child Kaftrio
If you forget to give your child a dose, work out how long it is since the missed dose.

- **If less than 6 hours** have passed since your child missed a dose, either morning or evening, give the forgotten dose as soon as possible. Then go back to your usual schedule.
- **If more than 6 hours** have passed:
    - **If your child missed a morning dose** of Kaftrio, give it as soon as you remember. Do not give the evening dose of ivacaftor. Give the next morning dose at the usual time.
    - **If your child missed an evening** dose of ivacaftor, do not give the missed dose. Wait for the next day and take the morning dose of Kaftrio as usual.

Do not give a double dose to make up for any missed doses.

If you stop giving your child Kaftrio
Give Kaftrio to your child for as long as your child's doctor recommends. Do not stop unless your child's doctor advises you to.

If you have any further questions on the use of this medicine, ask your child's doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects:

Possible signs of liver problems
Liver damage and worsening of liver function in people with or without liver disease. The worsening of liver function can be serious and may require transplantation (see section 2).
Increased liver enzymes in the blood are very common in patients treated with Kaftrio. These may be signs of liver problems:
- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Depression. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort (see section 2).

Tell your child's doctor straight away if he/she have any of these symptoms.

Very common side effects (may affect more than 1 in 10 people)
- Rash (more common in children, and in women compared to men)

Tell your child's doctor straight away if you notice a rash.

Other side effects:
Very common (may affect more than 1 in 10 people)
- Headache
- Dizziness
- Upper respiratory tract infection (common cold)
- Oropharyngeal pain (sore throat)
- Nasal congestion
- Stomach or abdominal pain
- Diarrhoea
- Increased liver enzymes (signs of stress on the liver)
- Changes in the type of bacteria in mucus
- Increased creatine phosphokinase (sign of muscle breakdown) seen in blood tests

Common (may affect up to 1 in 10 people)
- Flu
- Abnormal breathing (shortness of breath or difficulty breathing)
- Low blood sugar (hypoglycaemia)
- Runny nose
- Sinus problems (sinus congestion)
- Redness or soreness in the throat
- Ear problems: ear pain or discomfort, ringing in the ears, inflamed eardrum
- Spinning sensation (inner ear disorder)
- Wind (flatulence)
- Spots (acne)
- Itchy skin
- Breast mass
- Feeling nauseous

Uncommon (may affect up to 1 in 100 people)
- Breast and nipple problems: inflammation, pain
- Enlargement of the breast in men
- Increases in blood pressure
- Wheezing
- Blocked ears (ear congestion)

Not known (frequency cannot be estimated from the available data)
- Allergic reactions (hypersensitivity)
- Damage to the liver (liver injury)
- Raised bilirubin measurement (liver blood test)
- Behavioural changes

Additional side effects in adolescents
Side effects in adolescents are similar to those observed in adults.

Additional side effects in children
Most cases of behavioural changes have been reported in younger children aged 2-5 years.

Reporting of side effects
If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kaftrio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the sachet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your child's pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Kaftrio contains
- The active substances are ivacaftor, tezacaftor and elexacaftor.

Kaftrio 60 mg/40 mg/80 mg granules
Each sachet contains 60 mg of ivacaftor, 40 mg of tezacaftor and 80 mg of elexacaftor.

Kaftrio 75 mg/50 mg/100 mg granules
Each sachet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

- The other ingredients are: silica colloidal anhydrous (E551), croscarmellose sodium (E468), hypromellose (E464), hypromellose acetate succinate, lactose monohydrate, magnesium stearate (E470b), mannitol (E421), sodium laurilsulfate (E487), and sucralose (E955).

See the end of section 2 for important information about the contents of Kaftrio.

What Kaftrio looks like and contents of the pack
Kaftrio 60 mg/40 mg/80 mg granules are white to off-white granules in a sealed sachet.

Kaftrio 75 mg/50 mg/100 mg granules are white to off-white granules in a sealed sachet.

Kaftrio is available in pack size of 28 sachets (4 weekly wallets, each with 7 sachets).

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.