

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 $>5 \times$ the upper limit of normal (ULN), or ALT or AST $>3 \times$ ULN with total bilirubin $>2 \times$ 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.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); 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 $>3 \times$ 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 $>5 \times$ 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 $>3 \times \text{ULN}$ were 0.0%, 1.5%, and 10.6%, respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation $>3 \times \text{ULN}$ associated with elevated total bilirubin $>2 \times \text{ULN}$ 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 $>3 \times \text{ULN}$ were 1.3%, 2.7%, and 8.0% respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation $>3 \times \text{ULN}$ associated with elevated total bilirubin $>2 \times \text{ULN}$ 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 (ppFEV₁) 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

HPRA Pharmacovigilance

Website: www.hpra.ie

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: <i>CFTR</i> mutations identified to be responsive to IVA/TEZ/ELX based on clinical and/or <i>in vitro</i> data				
293A→G	E1433K	I1023R	P1013H	S1251N
314del9	E193K	I1051V	P1013L	S1255P
546insCTA	E217G	I105N	P1021L	S1362N
548insTAC	E257G	I1139V	P1021T	S158G
711+3A→G*	E264V	I119M	P1050A	S158N
1140-1151dup	E279D	I119V	P111A	S158R
1461insGAT	E282D	I1203V	P111L	S158T
1507_1515del9	E292K	I1230T	P1372T	S182R
2055del9	E384K	I1234L	P140S	S308P
2183A→G	E403D	I1234V	P205S	S341P
2789+5G→A*	E474K	I125T	P355L	S364P
2851A/G	E479D	I1269N	P41R	S42F
3007del6	E527G	I1366N	P439S	S434P
3132T→G	E528A	I1366T	P477S	S485C
3141del9	E56K	I148L	P499A	S492F
3143del9	E588K	I148N	P499S	S50P
3272-26A→G**	E588V	I175V	P5L†	S519G
3331del6	E60K	I203M	P574H	S531P
3410T→C	E725K	I331N	P574R	S549I
3523A→G	E822K	I336K	P67L*	S549N
3601A→C	E826K	I336L	P731L	S549R*
3761T→G	E831X	I444S	P750L	S557F

3791C/T	E92K	I444T	P798S	S589I
3849+10kbC→T [†]	F1016S	I497S	P988R	S589N
3850G→A	F1052V	I502T	P99R	S624R
3978G→C	F1074L	I506L	Q1012P	S686Y
A1006E	F1078S	I506V	Q1209P	S737F
A1018E	F1099L	I506V;D1168G [‡]	Q1238R	S821G
A1025D	F1107L	I521S	Q1291H	S898R
A1067P	F1286S	I530N	Q1291R	S912L
A1067T	F191V	I539T	Q1309H	S912L;G1244V [‡]
A1067V	F200I	I556V	Q1313K	S912T
A107G	F311del	I586V	Q1352H	S912W
A1081V	F311L	I601F	Q151K	S945L [†]
A1087P	F312del	I616T	Q179K	S955P
A1136T	F433L	I618N	Q237E	S977F
A120T	F508C;S1251 N [‡]	I618T	Q237H	S977F;R1438W [‡]
A1285G	F508del*	I86M	Q237P	T1036I
A1285V	F508del;R1438W [‡]	I980K	Q2X	T1036N*
A1319E	F575Y	I982M	Q30P	T1057R
A1364V	F587I	I991M	Q359K;T360K [‡]	T1086A
A1374D	F587L	K1060T	Q359R	T1086I
A141D	F693L(TTG)	K1080Q	Q372H	T1246I
A1466S	F834L	K162E	Q493L	T1299I
A155P	F87L	K464E	Q493R	T1299K
A209S	F932S	K464N	Q552P	T1396P
A234D	F994C	K481E	Q715H	T338I
A234V	G1047D	K522E	Q799K	T351I
A238V	G1047R	K522Q	Q890R	T351S
A300D	G1061R	K536E	Q98P	T351S;R851L [‡]
A309D	G1069R	K564E	Q98R	T388M
A349V	G1123R	K598E	R1048G	T465I
A357T	G1127E	K68E	R1066C [†]	T501A
A455E [†]	G1173S	K951E	R1066G	T582I
A455V	G1237V	L100V	R1066H [†]	T582S
A457T	G1244E	L1011S	R1070P	T896I
A462P	G1244R	L1040F	R1070Q	T908N
A46D	G1247R	L1065R	R1070W	T990I
A46V	G1249E	L1077P [†]	R1097H	V1008D
A534E	G1249R	L102R;F1016S [‡]	R1128G	V1010D
A554E	G1265V	L1227S	R1162Q	V1108L
A566D	G126D	L1260P	R117C [†]	V1114L
A62P	G1298V	L1324P	R117C;G576A;R668C [‡]	V1153E
A872E	G1349D	L1335F	R117G	V11I
A959V	G149R;G576A;R668C [‡]	L1335P	R117H*	V1240G
A9V	G178E	L1339F	R117L	V1293G
C128R	G178R	L137P	R117L;L997F [‡]	V1293I
C1355F	G194R	L1388P	R117P	V1318A
c.1367_1369dupTTG	G194V	L145H	R1239S	V1415F
C225R	G213E	L145V	R1283G	V201M
C225Y	G213E;R668C [‡]	L1480P	R1283M	V232A
C491R	G213V	L159S	R1283S	V232D
C590Y	G226R	L15P	R1422W	V317A
C76W	G239R	L15P;L1253F [‡]	R1438W	V322M

C866W	G241W	L165S	R1453W	V392G
C866Y	G253R	L167R	R170C	V393L
CFTRdup1-3	G27E	L183I	R248K	V456A
CFTRdup22,23	G27R	L206W ⁺⁺	R248T	V456F
D110E	G314A	L210P	R258G	V520I
D110H	G314E	L227P	R297Q	V562I;A1006E [‡]
D110N	G314R	L293P	R31L	V562L
D112N	G424S	L327P	R334L	V591A
D1152A	G437D	L32P	R334Q	V603F
D1152H ⁺⁺	G461R	L333F	R334W ⁺	V855I
D1154G	G461V	L333H	R347H [*]	V915L
D1154N	G463D	L346P	R347L	V920L
D1168G	G463V	L365P	R347P	V920M
D1270N [*]	G480C	L441P	R352G	V938G
D1270Y	G480D	L453S	R352Q	V93D
D1305E	G480S	L467F	R352W	V93G
D1312G	G500D	L558F	R3M	W79R
D1377H	G544S	L568F	R516S	W1098C
D1445N	G545R	L619S	R553Q	W1282G
D192G	G551A	L633P	R555G	W1282R
D192N	G551D [*]	L636P	R55K	W202C
D249Y	G551R	L88S	R600S	W361R
D373N	G551S	L927P	R709Q	W496R
D426N	G576A;R668C [‡]	L967F;L1096R [‡]	R74Q	Y1014C
D443Y	G576A;S1359Y [‡]	L973F	R74Q;R297Q [‡]	Y1014DEL
D443Y;G576A;R668C [‡]	G622D	L986P	R74Q;V201M;D1270N [‡]	Y1032C
D44G	G622V	M1028R	R74W	Y1032N
D529G	G628A	M1101K ⁺⁺	R74W;D1270N [‡]	Y1073C
D537N	G628R	M1137R	R74W;R1070W;D1270N [‡]	Y1092H
D565G	G723V	M1137V	R74W;S945L [‡]	Y109H
D567N	G85E ⁺⁺	M1157I	R74W;V201M [‡]	Y109N
D579G	G930E	M1210K	R74W;V201M;D1270N [‡]	Y122C
D58H	G970D	M1354T	R74W;V201M;L997F [‡]	Y1381H
D58V	G970S	M150K	R74W;V201M;Q1268R [‡]	Y161C
D614G	G970V	M150R	R751L	Y161D
D651H	H1054D	M152L	R75L	Y161S
D651N	H1054Y	M152V	R75Q;L1065P [‡]	Y301C
D806G	H1079P	M265R	R75Q;N1088D [‡]	Y563N
D828G	H1085P	M348K	R75Q;S549N [‡]	Y569H
D891G	H1085R	M394L	R765S	Y577F
D924N	H1197L	M469V	R766K	Y84H
D979A	H1375N	M498I	R792G	Y89C
D979V	H1375P	M595V	R792Q	Y913S
D985H	H1375R	M952I	R810G	Y919C
D985Y	H139L	M952T	R851L	
D993A	H139R	M961L	R933G	
D993G	H139Y	N1088D	S1045Y	
D993Y	H146R	N1195T	S108F	
deltaM1140	H199Q	N1303I	S1118F	
E1104K	H199Y	N1303K [*]	S1141N	
E1104V	H609L	N186K	S1159F	
E1123del	H620P	N187K	S1159P	

<i>E1126K</i>	<i>H620Q</i>	<i>N287K</i>	<i>S1188L</i>	
<i>E116K</i>	<i>H939R</i>	<i>N287Y</i>	<i>S1188P</i>	
<i>E116Q</i>	<i>H939R;H949L[‡]</i>	<i>N396Y</i>	<i>S13F</i>	
<i>E1221V</i>	<i>H949L</i>	<i>N418S</i>	<i>S13P</i>	
<i>E1228K</i>	<i>H954P</i>	<i>N847S</i>	<i>S18I</i>	
<i>E1401G</i>		<i>N900K</i>	<i>S18N</i>	
<i>E1409K</i>				

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 ppFEV₁ at screening between 40-90%. The mean ppFEV₁ 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 ppFEV₁ at screening

between 40-90%. The mean ppFEV₁ 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 ppFEV₁ at screening between 40-90%. The mean ppFEV₁ 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 ppFEV₁ ≥40% and weighed ≥15 kg at screening. The mean ppFEV₁ 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 ppFEV₁ ≥70% [mean ppFEV₁ 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 <i>CFTR</i> mutations				
<i>2789+5G>A</i>	<i>D1152H</i>	<i>L997F</i>	<i>R117C</i>	<i>T338I</i>
<i>3272-26A>G</i>	<i>G85E</i>	<i>M1101K</i>	<i>R347H</i>	<i>V232D</i>
<i>3849+10kbC>T</i>	<i>L1077P</i>	<i>P5L</i>	<i>R347P</i>	
<i>A455E</i>	<i>L206W</i>	<i>R1066H</i>	<i>S945L</i>	

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 ppFEV₁ $\geq 40\%$ and $\leq 100\%$ and aged 6 years or older at screening. The mean ppFEV₁ 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 ppFEV₁ 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 $\geq 3 \times$ ULN, or total bilirubin $\geq 2 \times$ ULN), were excluded. In study 445-111, patients who had ALT or AST $\geq 2 \times$ 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 ppFEV₁ from baseline through week 24. Treatment with IVA/TEZ/ELX in combination with IVA compared to placebo resulted in statistically significant improvement in ppFEV₁ of 14.3 percentage points (95% CI: 12.7, 15.8; $P < 0.0001$) (see Table 7). Mean improvement in ppFEV₁ was observed at the first assessment on day 15 and sustained through the 24-week treatment period. Improvements in ppFEV₁ were observed regardless of age, baseline ppFEV₁, sex, and geographic region.

A total of 18 patients receiving IVA/TEZ/ELX in combination with IVA had ppFEV₁ < 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 ppFEV₁ 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)	NA	14.3 (12.7, 15.8)
	P value	NA	P < 0.0001
	Within-group change (SE)	-0.4 (0.5)	13.9 (0.6)
Key secondary			
Absolute change in ppFEV ₁ from baseline at week 4 (percentage points)	Treatment difference (95% CI)	NA	13.7 (12.0, 15.3)
	P value	NA	P < 0.0001
	Within-group change (SE)	-0.2 (0.6)	13.5 (0.6)
Number of pulmonary exacerbations from baseline through week 24*	Number of events (event rate per year [†])	113 (0.98)	41 (0.37)
	Rate ratio (95% CI)	NA	0.37 (0.25, 0.55)
	P value	NA	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)	NA	-41.8 (-44.4, -39.3)
	P value	NA	P < 0.0001
	Within-group change (SE)	-0.4 (0.9)	-42.2 (0.9)
Absolute change in sweat chloride from baseline at week 4 (mmol/L)	Treatment difference (95% CI)	NA	-41.2 (-44.0, -38.5)
	P value	NA	P < 0.0001
	Within-group change (SE)	0.1 (1.0)	-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)	NA	20.2 (17.5, 23.0)
	P value	NA	P < 0.0001
	Within-group change (SE)	-2.7 (1.0)	17.5 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at week 4 (points)	Treatment difference (95% CI)	NA	20.1 (16.9, 23.2)
	P value	NA	P < 0.0001
	Within-group change (SE)	-1.9 (1.1)	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)	NA	1.04 (0.85, 1.23)
	P value	NA	P < 0.0001
	Within-group change (SE)	0.09 (0.07)	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 ppFEV₁ 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 ppFEV₁ of

10.0 percentage points (95% CI: 7.4, 12.6; $P < 0.0001$) (see Table 8). Improvements in ppFEV₁ were observed regardless of age, sex, baseline ppFEV₁, 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 ppFEV₁ 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)	NA	10.0 (7.4, 12.6)
	<i>P</i> value	NA	$P < 0.0001$
	Within-group change (SE)	0.4 (0.9)	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)	NA	-45.1 (-50.1, -40.1)
	<i>P</i> value	NA	$P < 0.0001$
	Within-group change (SE)	1.7 (1.8)	-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)	NA	17.4 (11.8, 23.0)
	<i>P</i> value	NA	$P < 0.0001$
	Within-group change (SE)	-1.4 (2.0)	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 ppFEV₁ 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 ppFEV₁ from baseline of 3.7 percentage points (95% CI: 2.8, 4.6; $P < 0.0001$) (see Table 9). Overall improvements in ppFEV₁ were observed regardless of age, sex, baseline ppFEV₁, 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 ppFEV₁ 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 ppFEV₁ 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 ppFEV₁ 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)	NA	9.2 (7.2, 11.3)
	P value	NA	P < 0.0001
	Within-group change (SE)	-0.4 (0.8)	8.9 (0.6)
Secondary			
Absolute change in sweat chloride from baseline through week 24 (mmol/L)	Treatment difference (95% CI)	NA	-28.3 (-32.1, -24.5)
	P value	NA	P < 0.0001
	Within-group change (SE)	0.5 (1.6)	-27.8 (1.1)
Absolute change in CFQ-R respiratory domain score from baseline through week 24 (points)	Treatment difference (95% CI)	NA	19.5 (15.5, 23.5)
	P value	NA	P < 0.0001
	Within-group change (SE)	-2.0 (1.6)	17.5 (1.2)
Absolute change from baseline in BMI at week 24 (kg/m ²)	Treatment difference (95% CI)	NA	0.47 (0.24, 0.69)
	P value	NA	P < 0.0001
	Within-group change (SE)	0.35 (0.09)	0.81 (0.07)
Absolute change from baseline in weight at week 24 (kg)	Treatment difference (95% CI)	NA	1.3 (0.6, 1.9)
	P value	NA	P < 0.0001
	Within-group change (SE)	1.2 (0.3)	2.4 (0.2)
Number of PEx through week 24	Rate ratio (95% CI)	NA	0.28 (0.15, 0.51)
	P value	NA	P < 0.0001
	Number of events	40	21
	Estimated event rate per year	0.63	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 ppFEV₁ was 4.53% (95% CI: 3.5, 5.56). Almost all subgroups according to *CFTR* mutation that included ≥5 patients showed an improvement in ppFEV₁ 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 ppFEV₁, 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 ppFEV₁ 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_{0-24h, 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 ($\pm$ 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 ($\pm$ 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 $\text{AUC}_{0-\infty}$ 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_{0-24h, 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

Ellexacaftor

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

4 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

07/2026

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