SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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)

Orange, capsule-shaped tablet debossed with “T100” on one side and plain on the other (dimensions 7.9 mm x 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 *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see section 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 *F508del* mutation using a genotyping assay (see section 5.1).

Posology

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

Table 1: Dosing recommendation 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	-	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).

Concomitant use of ciprofloxacin is not expected to have a clinically relevant effect on the exposure of ivacaftor/tezacaftor/elexacaftor; therefore, no dose adjustment is recommended with concomitant use of ciprofloxacin (see section 4.5).

Table 2: Dosing schedule for concomitant use with moderate and strong CYP3A inhibitors	
Moderate CYP3A Inhibitors	**Strong CYP3A Inhibitors**
Alternate each day: • Two ivacaftor/tezacaftor/elexacaftor (IVA/TEZ/ELX) tablets on the first day • One ivacaftor (IVA) tablet on the next day No evening IVA tablet dose.	Two IVA/TEZ/ELX tablets twice a week, approximately 3 to 4 days apart. No evening IVA 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

Mild (Child-Pugh Class A)	**Moderate (Child-Pugh Class B)**	**Severe (Child-Pugh Class C)**
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 IVA/TEZ/ELX tablets in the morning • Day 2: one IVA/TEZ/ELX tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. The evening dose of the IVA tablet 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 in children aged less than 2 years have not yet been established.

No data are available (see section 5.1).

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

In a patient with cirrhosis and portal hypertension liver failure leading to transplantation has been reported while receiving IVA/TEZ/ELX in combination with ivacaftor. IVA/TEZ/ELX in combination with IVA should be used with caution in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment (see sections 4.2, 4.8, and 5.2).

Elevated transaminases are common in patients with CF and have been observed in some patients treated with IVA/TEZ/ELX in combination with IVA. 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. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered (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).

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).

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

The incidence of rash events was higher in females than in males, particularly in females taking hormonal contraceptives. 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).

Mood disturbances

Effects on mood and behaviour have been reported in patients treated with IVA/TEZ/ELX, usually occurring within three months of treatment initiation. Patients (and caregivers) should be alerted about the need to monitor for symptoms including new onset or worsening of anxiety or low mood, sleep disturbance, and forgetfulness. In some children, persistent behavioural changes have been observed while taking IVA/TEZ/ELX. Inform patients to seek medical advice as soon as possible if these symptoms present.

Consider whether treatment discontinuation is appropriate.

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 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
Exposure to 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
IVA/TEZ/ELX 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

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use 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

It is unknown whether ELX, TEZ, IVA, or their metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of ELX, TEZ and IVA into the milk of lactating female rats (see section 5.3). A risk to the newborns/infants cannot be excluded. 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%) and upper respiratory tract infection (11.9%).

Serious adverse reactions of rash were reported in 3 (1.5%) patients treated with IVA/TEZ/ELX in combination with IVA compared to 1 (0.5%) in placebo.

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
Metabolism and nutrition disorders	Hypoglycaemia*	common
Psychiatric disorders	Low mood	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,	common

Table 4: Adverse reactions		
MedDRA System Organ Class	**Adverse Reactions**	**Frequency**
	Pharyngeal erythema, Abnormal breathing*	
	Wheezing*	uncommon
Gastrointestinal disorders	Diarrhoea*, Abdominal pain*	very common
	Nausea, Abdominal pain upper*, Flatulence*	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*, Aspartate aminotransferase increased*	common
	Liver injury†,Total bilirubin elevations†	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	very common
	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 elevations) reported from post-marketing data with IVA/TEZ/ELX in combination with IVA. This also included liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension. 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 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 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.

Description of selected adverse reactions

Transaminase elevations

In study 445-102, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the ULN was 1.5%, 2.5%, and 7.9% in 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.

Post-marketing cases of treatment discontinuation due to elevated transaminases have been reported (see section 4.4).

Rash events
In study 445-102, the incidence of rash events (e.g., rash, rash pruritic) was 10.9% in IVA/TEZ/ELX- and 6.5% in placebo-treated patients. The rash events were generally mild to moderate in severity. 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).

Increased creatine phosphokinase
In study 445-102, the incidence of maximum creatine phosphokinase >5 x 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 , and 445-111 was evaluated in 228 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 x ULN were 0.0%, 1.5%, and 10.6%, respectively. No IVA/TEZ/ELX-treated patients had transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN or discontinued treatment due to transaminase elevations (see section 4.4).

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

Age-appropriate formulation and strengths are available for children aged 2 to less than 6 years. Refer to the Summary of Product Characteristics for Kaftrio granules.

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 F508del-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 F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. With regard to non-F508del CFTR variant**s** on the second allele, it is not clear whether and to what extent the combination of ELX, TEZ and IVA also increases the amount of these mutated CFTR variant**s** on the cell surface and potentiates its channel open probability (or gating).

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 were 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).
[‡]The through week 24 endpoint is analyzed using mixed model with repeated measures (MMRM) including data from week 4, week 12 and week 24.
[†]The through week 12 endpoint is analyzed using MMRM including data from week 4 and week 12.
[□]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 $P<0.0001$).

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. Not all F508del heterozygotes have been clinically evaluated with IVA/TEZ/ELX in combination with IVA.

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 were dosed during the treatment period. 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.

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 drugs. Patients had a confirmed diagnosis of CF.

In studies 445-102, 445-103, 445-104, and 445-106 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 x ULN, or total bilirubin ≥2 x ULN), were excluded.

Patients in studies 445-102 and 445-103 were eligible to roll over into the 192-week open-label extension study (Study 445-105). Patients in studies 445-104, 445-106 and 445-116 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 5). 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 5 for a summary of primary and key secondary outcomes.

Table 5: 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 6). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ geographic region.

See Table 6 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 6: 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 7). 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 7 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 7: 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 in $ppFEV_1$ and other efficacy endpoints (see Table 8).

Table 8: 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.

* Baseline: parent study baseline.

† For subjects who were randomized 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 randomized 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).

Paediatric population

Paediatric patients aged 6 to <12 years

Study 445-106

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

In study 445-106 the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints were evaluation of pharmacokinetics, and efficacy including absolute change in $ppFEV_1$, sweat chloride (also see section 5.1), and $LCI_{2.5}$ from baseline through week 24; and measure of growth parameters (weight-for-age z-score, height-for-age z-score) from baseline at week 24. See Table 9 for a summary of secondary efficacy outcomes.

Table 9: 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)
Sweat chloride (mmol/L)	n=62 102.2 (9.1)	n=59[†] -58.6 (-61.1, -56.1)	n=60[‡] -60.9 (-63.7, -58.2)
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) [¶]
$LCI_{2.5}$	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; LCI: Lung Clearance Index.

[□] 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.

[†] The through week 12 endpoint is analyzed using MMRM including data from week 4, week 8 (for $ppFEV_1$) and week 12.

[‡] The through week 24 endpoint is analyzed using MMRM including data from week 4, week 8 (for $ppFEV_1$), week 12, week 16 (for $ppFEV_1$) and week 24.

[§] At week 12 endpoint.

[¶] At week 24 endpoint.

Study 445-107

Study 445-107 was 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. Final analysis was conducted in 64 paediatric patients aged 6 years and older and showed sustained improvements in $ppFEV_1$, SwCl, CFQ-R RD score, and $LCI_{2.5}$, consistent with the results observed in the study 445-106. Secondary efficacy endpoints of the final analysis are summarized in Table 10.

Table 10: Secondary efficacy analysis, full analysis set (N=64) (study 445-107)

Analysis	Statistic	Absolute change from baseline* at week 96	Absolute change from baseline* at week 192
$ppFEV_1$ (percentage points)	n	45	27
	LS mean	**11.2**	**9.6**
	95% CI	(8.3, 14.2)	(5.4, 13.7)
SwCl (mmol/L)	n	56	35
	LS mean	**-62.3**	**-57.9**
	95% CI	(-65.9, - 58.8)	(-63.3, -52.5)
CFQ-R RD score (points)	n	59	36
	LS mean	**13.3**	**10.0**
	95% CI	(11.4, 15.1)	(6.9, 13.0)
$LCI_{2.5}$	n	35	25
	LS mean	**-2.00**	**-2.33**
	95% CI	(-2.45, -1.55)	(-2.87, -1.79)
BMI-for-age z-score	n	60	39
	LS mean	**0.24**	**0.39**
	95% CI	(0.11, 0.37)	(0.19, 0.59)
Height-for-age z-score	n	60	39
	LS mean	**0.06**	**0.04**
	95% CI	(-0.03, 0.16)	(-0.12, 0.19)
Body weight-for-age z-score	n	60	39
	LS mean	**0.23**	**0.38**
	95% CI	(0.10, 0.35)	(0.20, 0.55)
PEx during the Cumulative Triple Combination (TC) Efficacy Period†	Number of events	7	11
	Observed event rate per year	0.04	0.045

$ppFEV_1$: 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.
* Baseline: parent study baseline.
† The Cumulative TC Efficacy Period includes data from the 66 patients who were enrolled and received at least of one dose of treatment in the parent study (study 445-106 Part B) and/or received at least one dose during study 445-107.

Study 445-116
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).

The Medicines and Healthcare products Regulatory Agency (MHRA) 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 9.

Table 11: Mean (SD) pharmacokinetic parameters of ELX, TEZ and IVA at steady state in patients with CF aged 12 years and older

	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).

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 12. 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 12. Mean (SD) ELX, 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)	TEZ $AUC_{0\text{-}24h,ss}$ (µg·h/mL)	IVA $AUC_{0\text{-}12h,ss}$ (µg·h/mL)
Patients aged 2 to <6 years, <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)	87.3 (17.3)	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)	90.2 (27.9)	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)	67.0 (22.3)	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)	103 (23.7)	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)	88.8 (21.8)	10.6 (3.35)

Table 12. Mean (SD) ELX, 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)**	**TEZ $AUC_{0\text{-}24h,ss}$ (µg·h/mL)**	**IVA $AUC_{0\text{-}12h,ss}$ (µg·h/mL)**
Adult patients (≥18 years) (N=179)	IVA 150 mg q12h/ TEZ 100 mg qd/ ELX 200 mg qd	168 (49.9)	89.5 (23.7)	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 not relevant for the indicated paediatric population 6 to 11 years of age, 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 animals studies
Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through day 35 at IVA exposure levels of 0.21 times 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

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)/PVC (polyvinyl chloride) and sealed with an aluminium 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 (Europe) Limited
2 Kingdom Street
London, W2 6BD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 22352/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2025

10 DATE OF REVISION OF THE TEXT

14/01/2026