▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Alyftrek 50 mg/20 mg/4 mg film-coated tablets
Alyftrek 125 mg/50 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alyftrek 50 mg/20 mg/4 mg film-coated tablets

Each film-coated tablet contains 50 mg of deutivacaftor, 20 mg of tezacaftor, and vanzacaftor calcium dihydrate equivalent to 4 mg of vanzacaftor.

Alyftrek 125 mg/50 mg/10 mg film-coated tablets

Each film-coated tablet contains 125 mg of deutivacaftor, 50 mg of tezacaftor, and vanzacaftor calcium dihydrate equivalent to 10 mg of vanzacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Alyftrek 50 mg/20 mg/4 mg film-coated tablets

Purple, round-shaped tablet debossed with “V4” on one side and plain on the other (7.35 mm diameter).

Alyftrek 125 mg/50 mg/10 mg film-coated tablets

Purple, capsule-shaped tablet debossed with “V10” on one side and plain on the other (15 mm × 7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Alyftrek should only be prescribed by healthcare professionals with experience in the treatment of CF. If the person with CF has an unknown genotype, 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 genotyping assay) (see section 5.1). Alyftrek should only be used in people diagnosed with CF. A diagnosis of CF should be made based on diagnostic guidelines and clinical judgement.

There are a limited number of people with CF who harbour mutations not listed in Table 4 that may be responsive to treatment. In these cases, treatment can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision. This excludes people with CF 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).

Posology

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).

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

Table 1: Dosing recommendation for people with CF aged 6 years and older

Age	Weight	Daily dose (once daily)
≥ 6 years	< 40 kg	Three tablets of deutivacaftor 50 mg/tezacaftor 20 mg/vanzacaftor 4 mg
	≥ 40 kg	Two tablets of deutivacaftor 125 mg/tezacaftor 50 mg/vanzacaftor 10 mg

Each dose should be taken in its entirety with fat-containing food, once daily at approximately the same time each day (see Method of administration).

Missed dose

If 6 hours or less have passed since the missed dose, the missed dose should be taken as soon as possible, and the original schedule should be continued the next day.

If more than 6 hours have passed since the missed dose, the missed dose should be skipped, and the original schedule should be continued the next day.

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, or clarithromycin), the dose should be reduced as recommended in Table 2 (see sections 4.4 and 4.5).

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

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
≥ 6 years	< 40 kg	Two tablets of deutivacaftor 50 mg/tezacaftor 20 mg/ vanzacaftor 4 mg every other day	Two tablets of deutivacaftor 50 mg/ tezacaftor 20 mg/vanzacaftor 4 mg once a week
	≥ 40 kg	One tablet of deutivacaftor 125 mg/tezacaftor 50 mg/ vanzacaftor 10 mg every other day	One tablet of deutivacaftor 125 mg/ tezacaftor 50 mg/vanzacaftor 10 mg once a week

Special populations

Elderly

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

Hepatic impairment

Mild hepatic impairment (Child-Pugh Class A)

No dose adjustment is recommended. Liver function tests should be closely monitored (see sections 4.4, 4.8, and 5.2).

Moderate hepatic impairment (Child-Pugh Class B)

Use not recommended. D-IVA/TEZ/VNZ should only be considered when there is a clear medical need, and the benefit outweighs the risk. If used, no dose adjustment is recommended. Liver function tests should be closely monitored (see sections 4.4, 4.8, and 5.2).

Severe hepatic impairment (Child-Pugh Class C)

Should not be used (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is recommended for people with CF who have mild or 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 D-IVA/TEZ/VNZ in children aged less than 6 years have not yet been established. No clinical trial data are available. D-IVA/TEZ/VNZ should not be used in children less than 1 year of age because of safety-related findings in juvenile rat studies with tezacaftor (see section 5.3).

Method of administration

For oral use. People with CF 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.

Tablets 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 (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 taking a medicinal product containing elexacaftor, tezacaftor, and ivacaftor, which contains one same (tezacaftor) and one similar (ivacaftor) active ingredient as Alyftrek. Elevated transaminases are common in people with CF and have been observed in some people with CF treated with D-IVA/TEZ/VNZ (see section 4.8). In patients taking IVA/TEZ/ELX in combination with IVA, transaminase elevations have sometimes been associated with concomitant elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all people with CF prior to initiating treatment, every 3 months during the first year of treatment, and annually thereafter. For people with CF with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Treatment should be interrupted, and serum transaminases and total bilirubin should be promptly measured if a patient develops clinical signs or symptoms suggestive of liver injury (e.g., jaundice and/or dark urine, unexplained nausea or vomiting, right upper quadrant pain, or anorexia). Dosing should be interrupted in the event of ALT or AST > 5 × the upper limit of normal (ULN), or ALT or AST > 3 × ULN with bilirubin > 2 × ULN. Laboratory tests should be closely followed until the abnormalities resolve. Following resolution, the benefits and risks of resuming treatment should be considered (see sections 4.2, 4.8, and 5.2). Patients who resume treatment after interruption should be monitored closely.

In people with CF with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) D-IVA/TEZ/VNZ should be used with caution 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).

Patients who discontinued or interrupted a medicinal product containing tezacaftor or ivacaftor due to adverse reactions

There are no available safety data for D-IVA/TEZ/VNZ in patients who previously discontinued or interrupted treatment with a medicinal product containing tezacaftor or ivacaftor due to adverse reactions. The benefits and risks should be considered before using D-IVA/TEZ/VNZ in these patients. If D-IVA/TEZ/VNZ is used in these patients, they should be closely monitored, as clinically appropriate.

Hepatic impairment

Treatment of patients with moderate hepatic impairment is not recommended. For people with CF with moderate hepatic impairment, the use of D-IVA/TEZ/VNZ should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, no dose adjustment is needed.

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

Depression and other psychiatric disorders

Depression and anxiety have been reported in patients treated with D-IVA/TEZ/VNZ.

In some cases, symptom improvement was reported after treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts,

insomnia, anxiety, or unusual changes in behaviour and instruct them to notify their physician if these symptoms occur (see section 4.8).

Renal impairment

There is no experience with D-IVA/TEZ/VNZ in people with CF 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 treatment.

Clinical studies comparing D-IVA/TEZ/VNZ to TEZ/IVA or IVA

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

Patients after organ transplantation

D-IVA/TEZ/VNZ has not been studied in people with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. If used, 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 people with CF taking hormonal contraceptives who develop rash, interrupting treatment with D-IVA/TEZ/VNZ and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming D-IVA/TEZ/VNZ without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered (see sections 4.5 and 4.8).

Elderly

Clinical studies of D-IVA/TEZ/VNZ did not include sufficient number of people with CF 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 ivacaftor (IVA), and ivacaftor (IVA) monotherapy (see sections 4.2 and 5.2).

Interactions with medicinal products

CYP3A inducers

Exposures to vanzacaftor (VNZ), tezacaftor (TEZ) and deutivacaftor (D-IVA) are expected to decrease with the concomitant use of moderate or strong CYP3A inducers, potentially resulting in the reduction of D-IVA/TEZ/VNZ efficacy; therefore, co-administration with moderate or strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

Exposure to VNZ, TEZ and D-IVA are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see sections 4.2 and 4.5).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in people with CF aged less than 18 years treated with ivacaftor (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. As D-IVA is a deuterated isotopologue of IVA, baseline and follow-up ophthalmological examinations are recommended in people with CF aged less than 18 years initiating treatment with D-IVA/TEZ/VNZ (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 D-IVA/TEZ/VNZ

CYP3A inducers

VNZ, TEZ and D-IVA are substrates of CYP3A. VNZ and D-IVA are sensitive substrates of CYP3A. Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced D-IVA/TEZ/VNZ efficacy. Co-administration with moderate or strong CYP3A inducers is not recommended (see section 4.4).

Examples of moderate or strong CYP3A inducers include:

- rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*), and efavirenz

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased VNZ AUC by 10.5-fold, TEZ AUC by 4.0- to 4.5-fold and D-IVA AUC by 11.1-fold. The dose of D-IVA/TEZ/VNZ should be reduced when co-administered with strong CYP3A inhibitors (see sections 4.2 and 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 may increase VNZ, TEZ, and D-IVA AUC by approximately 2.4- to 3.9-fold, 2.1-fold, and 2.9- to 4.8-fold, respectively. The dose of D-IVA/TEZ/VNZ should be reduced when co-administered with moderate CYP3A inhibitors (see sections 4.2 and 4.4).

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin
- verapamil

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

Ciprofloxacin

D-IVA/TEZ/VNZ 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 VNZ or D-IVA. Therefore, no dose adjustment is necessary during concomitant administration of D-IVA/TEZ/VNZ with ciprofloxacin.

Medicinal products affected by VNZ, TEZ, and D-IVA

CYP2C9 substrates

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

Potential for interaction with transporters

D-IVA/TEZ/VNZ was not evaluated for concomitant use with P-glycoprotein (P-gp) substrates. However, co-administration of tezacaftor/ivacaftor (TEZ/IVA) with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold. Administration of D-IVA/TEZ/VNZ 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.

Based on *in vitro* data, VNZ, TEZ, and D-IVA have low potential to inhibit OATP1B1 at clinically relevant concentrations. D-IVA has a similar OATP1B1 inhibition potential to IVA *in vitro*. Co-administration of TEZ/IVA with pitavastatin, an OATP1B1 substrate, had no clinically relevant effect on the exposure of pitavastatin.

Breast Cancer Resistance Protein (BCRP) substrates

VNZ and D-IVA are inhibitors of BCRP *in vitro*. Concomitant use of D-IVA/TEZ/VNZ with BCRP substrates may increase exposure of these substrates; however, this has not been studied clinically. When administered concomitantly with substrates of BCRP, caution and appropriate monitoring should be used.

Hormonal contraceptives

D-IVA/TEZ/VNZ was not evaluated for concomitant use with oral contraceptives. TEZ in combination with IVA and IVA alone have been studied with ethinyl estradiol/norethindrone and were found to have no clinically relevant effect on the exposures of the oral contraceptive. VNZ, TEZ, and D-IVA have low potential to induce or inhibit CYP3A *in vitro*. D-IVA/TEZ/VNZ 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 D-IVA/TEZ/VNZ 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 Alyftrek during pregnancy.

Breast-feeding

Limited data show that TEZ is excreted in human milk and has been quantified in plasma of breastfed newborns/infants of treated women. VNZ is excreted into the milk of lactating female rats. The effect of D-IVA has not been evaluated, however, limited data show that IVA is excreted in human milk and has been quantified in plasma of breastfed newborns/infants of treated women.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Alyftrek 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 VNZ, TEZ, and D-IVA on fertility in humans. The effects of D-IVA on fertility have not been evaluated in rats; however, IVA had an effect on fertility in female and male rats. VNZ and TEZ had no effects on fertility and reproductive performance indices in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

D-IVA/TEZ/VNZ has a minor influence on the ability to drive or use machines. Dizziness has been reported in people with CF receiving TEZ/IVA in combination with IVA as well as IVA monotherapy (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 in people with CF aged 12 years and older treated with Alyftrek include headache (15.8%) and diarrhoea (12.1%). The frequency of treatment discontinuation, in clinical trials, due to adverse reactions is 3.8%. The most common adverse reactions leading to treatment discontinuation were alanine aminotransferase increased (1.5%) and aspartate aminotransferase increased (1.3%).

The most common serious adverse reactions that occurred with Alyftrek are ALT increased (0.4%) and AST increased (0.4%).

Tabulated list of adverse reactions

Table 3 reflects adverse reactions observed with D-IVA/TEZ/VNZ, TEZ/IVA in combination with IVA, and IVA monotherapy. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 3: Adverse Drug Reactions by Preferred Term, Incidence and Frequency		
System organ class	**Adverse reactions**	**Frequency**
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Influenza*	very common
	Rhinitis	common
Psychiatric disorders	Depression*	common
	Anxiety*	common
Nervous system disorders	Headache*	very common
	Dizziness	very common
Ear and labyrinth disorders	Ear pain	common
	Ear discomfort	common
	Tinnitus	common
	Tympanic membrane hyperaemia	common
	Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	very common
	Nasal congestion	very common
	Sinus congestion	common
	Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea*	very common
	Nausea	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*	common
	Aspartate aminotransferase increased*	common
Skin and subcutaneous tissue disorders	Rash*	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon
Investigations	Bacteria in sputum	very common
	Blood creatine phosphokinase increased*	common

* Adverse reactions observed during clinical studies with deutivacaftor/tezacaftor/vanzacaftor.

Description of selected adverse reactions

Transaminase elevations

In Studies 121-102 and 121-103, the incidence of maximum transaminase (ALT or AST) > 8 ×, > 5 ×, or > 3 × the ULN was 1.3%, 2.5%, and 6.0% with D-IVA/TEZ/VNZ. The incidence of adverse reactions of transaminase elevations was 9.0% with D-IVA/TEZ/VNZ. Of the D-IVA/TEZ/VNZ-treated participants, 1.5% discontinued treatment for elevated transaminases.

In study 121-105, Cohort B1, in people with CF aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) > 8 ×, > 5 ×, and > 3 × ULN were 0%, 1.3%, and 3.8%, respectively.

Rash events

In Studies 121-102 and 121-103, the incidence of rash events (e.g., rash, rash pruritic) was 11.0% with D-IVA/TEZ/VNZ. The rash events were generally mild to moderate in severity. The incidence of rash events was 9.4% in males and 13.0% in females (see sections 4.4 and 4.5).

Increased creatine phosphokinase

In Studies 121-102 and 121-103, the incidence of maximum creatine phosphokinase > 5 × the ULN was 7.9% with D-IVA/TEZ/VNZ. Of the D-IVA/TEZ/VNZ-treated participants, 0.2% discontinued treatment for increased creatine phosphokinase.

Paediatric population

The safety data of D-IVA/TEZ/VNZ in study 121-105, Cohort B1 was evaluated in 78 people with CF aged 6 to less than 12 years. The safety data of D-IVA/TEZ/VNZ in study 121-102 and study 121-103 was evaluated in 67 people with CF aged 12 to less than 18 years. The safety profile is generally consistent among paediatric and adult patients.

Transaminase elevations

During study 121-105, Cohort B1, in people with CF aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) > 8 ×, > 5 ×, and > 3 × ULN was 0.0%, 1.3%, and 3.8%, respectively. No Alyftrek-treated patients had transaminase elevation > 3 × ULN associated with elevated total bilirubin > 2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

Rash

During study 121-105 in patients aged 6 to less than 12 years, 4 (5.1%) subjects had at least 1 rash event. The rash events were mild in severity. These rashes did not lead to discontinuation or interruption of treatment.

Lenticular opacity

During study 121-105 in patients aged 6 to less than 12 years, 1 (1.3%) person with CF had an event of lenticular opacity.

Other special populations

The safety profile of D-IVA/TEZ/VNZ was generally similar across all subgroups of patients, including analysis by age, gender, baseline percent predicted Forced Expiratory Volume in one second ($ppFEV_1$) and geographic regions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

No specific antidote is available for overdose with Alyftrek. 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: R07AX33

Mechanism of action

VNZ 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 select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. D-IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of VNZ, TEZ and D-IVA is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured both by CFTR mediated chloride transport *in vitro* and by sweat chloride (SwCl) in people with CF.

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

The chloride transport response of mutant CFTR protein to D-IVA/TEZ/VNZ was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. D-IVA/TEZ/VNZ 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 D-IVA/TEZ/VNZ based on *in vitro* data in FRT cells, will likely result in a clinical response.

Table 4 lists *CFTR* mutations included in the indication for treatment with Alyftrek. 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 4: *CFTR* mutations identified to be responsive to D-IVA/TEZ/VNZ based on clinical and/or *in vitro* data

1140-1151dup	E116K[#]	H939R;H949L[‡]	N396Y	S1159F[*]
1461insGAT	E116Q	H949L	N418S	S1159P[#]
1507_1515del9	E1221V	H954P	N847S	S1188L
1650C/G	E1228K	I1023R	N900K	S1188P
2055del9	E1401G	I105N	P1013H	S1251N[*]
2183A→G	E1409K	I1051V	P1013L	S1255P
2789+5G→A[†]	E1433K	I1139V[#]	P1021L	S13F
2851A/G	E193K[#]	I119M	P1021T	S13P
293A→G	E217G	I119V	P1050A	S1362N
3007del6	E257G	I1203V	P111A	S158G

3131del15	E264V	I1230T	P111L	S158N
3132T→G	E279D	I1234L	P1372T	S158R
3141del9	E282D	I1234Vdel6aa	P140S	S158T
3143del9	E292K	I125T	P205S[#]	S182R
314del9	E384K	I1269N[#]	P355L	S18I
3195del6	E403D[#]	I1366N[#]	P41R	S18N
3199del6	E474K	I1366T	P439S	S308P
3272-26A→G[†]	E479D	I1398S	P477S	S341P
3331del6	E527G	I148L	P499A	S364P
3410T→C	E528A	I148N	P499S	S42F
3523A→G	E56K[#]	I148T;H609R[‡]	P574H	S434P
3601A→C	E588K	I175V[#]	P5L[#]	S485C
3761T→G	E588V[#]	I203M	P67L[#]	S492F
3791C/T	E60K[#]	I331N	P731L	S50P
3849+10kbC→T[†]	E725K	I336K[*]	P750L	S519G
3850G→A	E822K[#]	I336L	P798S	S531P
3978G→C	E826K	I444S	P988R	S549I
4193T→G	E831X[†]	I444T	P99L	S549N[*]
546insCTA[#]	E92K[#]	I497S	P99R	S549R[*]
548insTAC	F1016S[#]	I502N	Q1012P	S557F
711+3A→G[†]	F1052V[#]	I502T[*]	Q1100P	S589I
A1006E[#]	F1074L[#]	I506L	Q1209P	S589N[#]
A1018E	F1078S	I506T	Q1238R	S624R
A1025D	F1099L[#]	I506V	Q1291H	S686Y
A1067P	F1107L	I506V;D1168G[‡]	Q1291R[#]	S737F[#]
A1067T[#]	F1286S	I521S	Q1309H	S821G
A1067V	F191V[#]	I530N	Q1313K	S898R
A107G	F200I	I539T	Q1352H	S912L[#]
A1081V	F311del[#]	I556V	Q151K	S912L;G1244V[‡]
A1087P	F311L[#]	I586V	Q179K	S912T
A1136T	F312del	I601F[#]	Q2X	S912W
A120T[#]	F433L	I601T	Q237E[#]	S945L[*]
A1285G	F508C;S1251N[‡ #]	I616T	Q237H[#]	S955P
A1285V	F508del[*]	I618N	Q237P	S977F[#]
A1319E	F508del;R1438W[‡]	I618T[#]	Q30P	S977F;R1438W[‡]
A1364V	F575Y[#]	I86M	Q359K/T360K[‡]	T1036I
A1374D	F587I	I980K[#]	Q359R[#]	T1036N[#]
A141D	F587L	I982M	Q372H	T1057R
A1466S	F693L(TTG)	I991M	Q452P	T1086A
A155P	F834L	K1060T[#]	Q493L	T1086I
A209S	F87L	K1080Q	Q493R	T1246I
A234D[#]	F932S	K162E	Q552P	T1299I
A234V	F994C	K464E	Q715H	T1299K
A238V	G1047D	K464N	Q799K	T1396P
A300D	G1047R	K481E	Q890R	T164P
A309D	G1061R	K522E	Q98P	T338I[#]
A349V[#]	G1069R[#]	K522Q	Q98R[#]	T351I
A357T	G1123R	K536E	R1048G	T351S
A455E[*]	G1127E	K564E	R1066C	T351S;R851L[‡]
A455V	G1173S	K598E	R1066G	T388M
A457P	G1237V	K68E	R1066H[*]	T465I
A457T	G1244E[*]	K951E	R1066L	T465N
A462P	G1244R	L100V	R1066M	T501A
A46D	G1247R	L1011S	R1066P	T582I
A46V	G1249E	L102R	R1070P	T582S

A534E	G1249R[#]	L102R;F1016S[‡]	R1070Q[#]	T604I
A554E[#]	G1265V	L1040F	R1070W[#]	T896I
A559T	G126D[#]	L1065P	R1097H	T908N
A559V	G1298V	L1065R	R1128G	T990I
A561E	G1349D[#]	L1077P[*]	R1162Q	V1008D
A566D	G149R	L1227S	R117C	V1010D
A613T	G149R;G576A;R668C[‡]	L1260P	R117C;G576A;R6	V1108L
A62P	G178E[#]	L1324P[#]	68C[‡]	V1114L
A72D	G178R[#]	L1335F	R117G[#]	V1153E[#]
A872E	G194R[#]	L1335P[#]	R117H	V11I
A959V	G194V[#]	L1339F	R117L[#]	V1240G[#]
A9V	G213E	L137P	R117L;L997F[‡]	V1293G[#]
C128R	G213E;R668C[‡]	L137R	R117P[#]	V1293I
C1355F	G213V	L1388P	R1239S	V1318A
c.1367_1369dupT	G226R	L145H	R1283G	V1415F
TG	G239R	L145V	R1283M[#]	V201M[#]
C225R	G241W	L1480P[#]	R1283S[#]	V232A
C225Y	G253R	L159S	R1422W	V232D[#]
C491R	G27E	L15P[#]	R1438W	V317A
C590Y	G27R	L15P;L1253F[‡]	R1453W	V322M
C76W	G314A	L165S	R170C	V392G
C866W	G314E[#]	L167R	R248K	V393L
C866Y	G314R	L183I	R248T	V456A
CFTRdup22,23	G424S	L206W[*]	R258G[#]	V456F
CFTRdup1-3	G437D	L210P	R297Q	V520F
D110E[#]	G451V	L227P	R31L[#]	V520I
D110H[#]	G461R	L293P	R334L[#]	V562I;A1006E[‡]
D110N	G461V	L327P	R334Q[#]	V562L
D112N	G463D	L32P	R334W[§]	V591A
D1152A	G463V	L333F	R347H[#]	V603F
D1152H[*]	G480C	L333H	R347L[#]	V855I
D1154G	G480D	L346P[#]	R347P[*]	V915L
D1154N	G480S	L365P	R352G	V920L
D1168G	G500D	L441P	R352Q[*]	V920M
D1270N[#]	G544S	L453S	R352W[#]	V93D
D1270Y	G545R	L467F	R3M	V938G
D1305E	G551A	L558F	R516G	V93G
D1312G	G551D[*]	L568F	R516S	W1098C[*]
D1377H	G551R	L594P	R553Q[#]	W1282G
D1445N	G551S[#]	L610S	R555G	W1282R[*]
D192G[#]	G576A;R668C[‡#]	L619S	R55K	W202C
D192N	G576A;S1359Y[‡]	L633P	R560S	W361R
D249Y	G622D[#]	L636P	R560T	W496R
D373N	G622V	L88S	R600S	W79R
D426N	G628A	L927P	R709Q	Y1014C[#]
D44G	G628R	L967F;L1096R[‡]	R74Q[#]	Y1014DEL
D443Y[#]	G723V	L973F	R74Q;R297Q[‡]	Y1032C[#]
D443Y;G576A;R6	G85E[*]	L986P	R74Q;V201M;D1	Y1032N
68C[‡#]	G85V	M1028R	270N[‡]	Y1073C
D513G	G91R	M1101K[*]	R74W[#]	Y1092H
D529G	G930E	M1101R	R74W;D1270N[‡#]	Y109C
D537N	G970D[#]	M1137R	R74W;R1070W;D	Y109H
D565G	G970S	M1137V	1270N[‡]	Y109N[#]
D567N	G970V	M1157I	R74W;S945L[‡]	Y122C
D572N	H1054D[*]	M1210K	R74W;V201M[‡#]	Y1381H

D579G[#]	H1054Y	M1354T	R74W;V201M;D1	Y161C
D58H	H1079P	M150K	270N[‡#]	Y161D
D58V	H1085P	M150R	R74W;V201M;L9	Y161S[#]
D614G[#]	H1085R	M152L	97F[‡]	Y301C
D651H	H1197L	M152V[#]	R74W;V201M;Q1	Y517C
D651N	H1375N	M265R[#]	268R[‡]	Y563N[*]
D806G	H1375P[#]	M348K	R751L[#]	Y569C
D828G	H1375R	M394L	R75L	Y569H
D891G	H139L	M469V	R75Q;L1065P[‡]	Y577F
D924N[#]	H139R	M498I	R75Q;N1088D[‡]	Y84H
D979A	H139Y	M595V	R75Q;S549N[‡]	Y89C
D979V[#]	H146R	M952I[#]	R765S	Y913C
D985H	H147del	M952T[#]	R766K	Y913S
D985Y	H147P	M961L	R792G[#]	Y919C
D993A	H199Q	N1088D	R792Q	
D993G	H199R	N1195T	R810G	
D993Y	H199Y	N1303I	R851L	
deltaM1140	H609L	N1303K[¶]	R933G[#]	
E1104K	H609R	N186K	S1045Y	
E1104V	H620P	N187K	S108F	
E1123del	H620Q	N287K	S1118F	
E1126K	H939R[#]	N287Y	S1141N	

There are people with CF harbouring two rare, non-*F508del CFTR* mutations not listed in Table 4. 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, Alyftrek 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.
[†] Non-canonical splice mutations where efficacy is extrapolated from clinical data from other CFTR modulators because these mutations are not amenable to FRT assay.
[‡] 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.
[¶] N1303K is extrapolated from clinical data from IVA/TEZ/ELX in combination with IVA and supported by Human Bronchial Epithelial (HBE) assay data.
[#] Mutations are extrapolated from FRT data with TEZ/IVA or IVA monotherapy in which a positive response is indicative of a clinical response.
[§] R334W is predicted to be responsive by extrapolation of clinical data from published literature with IVA/TEZ/ELX.

Non-annotated mutations are included based on the FRT assay with D-IVA/TEZ/VNZ in which a positive response is indicative of a clinical response.

Pharmacodynamic effects

Effects on sweat chloride

In study 121-102 (people with CF heterozygous for a *F508del* and a *CFTR* mutation 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)*, the treatment difference of D-IVA/TEZ/VNZ compared to IVA/TEZ/ELX for mean absolute change in SwCl from baseline through week 24 was -8.4 mmol/L (95% CI: -10.5, -6.3; *P* <0.0001).

In study 121-103 (people with CF homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to IVA/TEZ/ELX with no *F508del* mutation), the treatment difference of D-IVA/TEZ/VNZ compared to IVA/TEZ/ELX for mean absolute change in SwCl from baseline through week 24 was -2.8 mmol/L (95% CI: -4.7, -0.9; *P* = 0.0034).

In study 121-105, Cohort B1 (people with CF aged 6 to less than 12 years with at least one mutation that is responsive to IVA/TEZ/ELX), the mean absolute change in SwCl from baseline through week 24 was -8.6 mmol/L (95% CI: -11.0, -6.3).

Cardiovascular effects

Effect on QT interval

At exposures corresponding up to 6 times over those observed with the VNZ maximum recommended dose, and doses up to 3 times over the TEZ and D-IVA maximum recommended doses, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Clinical efficacy and safety

The efficacy of D-IVA/TEZ/VNZ in people with CF aged 12 years and older was evaluated in two, phase 3, randomised, double-blind, IVA/TEZ/ELX-controlled studies (Studies 121-102 and 121-103). The pharmacokinetic profile, safety, and efficacy of D-IVA/TEZ/VNZ in people with CF aged 6 to less than 12 years are supported with evidence from studies of D-IVA/TEZ/VNZ in people with CF aged 12 years and older (Studies 121-102 and 121-103) and additional data from an open-label, phase 3 study (study 121-105, Cohort B1).

Studies 121-102 and 121-103

Study 121-102 was a 52-week, randomised, double-blind, IVA/TEZ/ELX-controlled study in people with CF heterozygous for *F508del* and a *CFTR* mutation 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 total of 398 people with CF aged 12 years and older received IVA/TEZ/ELX during a 4-week run-in period and were then randomised to receive D-IVA/TEZ/VNZ or IVA/TEZ/ELX during the 52-week treatment period. The mean age was 30.8 years (range 12.2 years, 71.6 years; 14.3% aged under 18 years) and 41% female and 59% male. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 67.1 percentage points (range: 28.0, 108.6), the mean CFQ-R RD score at baseline was 84.4 (range 22.2, 100), and the mean SwCl at baseline was 53.9 mmol/L (range: 10.0 mmol/L, 113.5 mmol/L).

Study 121-103 was a 52-week, randomised, double-blind, IVA/TEZ/ELX-controlled study in people with CF who had one of the following genotypes: homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to IVA/TEZ/ELX with no *F508del* mutation. A total of 573 people with CF aged 12 years and older received IVA/TEZ/ELX during a 4-week run-in period and were then randomised to receive D-IVA/TEZ/VNZ or IVA/TEZ/ELX during the 52-week treatment period. The mean age was 33.7 years (range 12.2 years, 71.2 years; 13.8% aged under 18 years) and 48.9% female and 51.1% male. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 66.8 percentage points (range: 36.4, 112.5), the mean CFQ-R RD score at baseline was 85.7 (range 27.8, 100), and the mean SwCl at baseline was 42.8 mmol/L (range: 10.0 mmol/L, 113.3 mmol/L).

In both studies, the primary endpoint evaluated non-inferiority in mean absolute change from baseline in $ppFEV_1$ through week 24. The key secondary endpoint evaluated superiority in mean absolute change from baseline in SwCl through week 24.

See Table 5 for a summary of key efficacy outcomes for Studies 121-102 and 121-103.

Table 5: Efficacy analyses from study 121-102 and study 121-103					
Analysis*	**Statistic**	**Study 121-102**		**Study 121-103**	
		D-IVA/TEZ/VNZ N = 196	**IVA/TEZ/ELX N = 202**	**D-IVA/TEZ/VNZ N = 284**	**IVA/TEZ/ELX N = 289**
Primary					
Baseline $ppFEV_1$ (percentage points)	Mean (SD)	67.0 (15.3)	67.2 (14.6)	67.2 (14.6)	66.4 (14.9)
Absolute change from baseline in $ppFEV_1$ through week 24 (percentage points)	n	187	193	268	276
	LS mean (SE)	0.5 (0.3)	0.3 (0.3)	0.2 (0.3)	0.0 (0.2)
	LS mean difference, 95% CI	0.2 (-0.7, 1.1)		0.2 (-0.5, 0.9)	
	P-value (1-sided) for Non-Inferiority†	< 0.0001		< 0.0001	
Key Secondary					
Baseline SwCl (mmol/L)	Mean (SD)	53.6 (17.0)	54.3 (18.2)	43.4 (18.5)	42.1 (17.9)
Absolute change from baseline in SwCl through week 24 (mmol/L)	n	185	194	270	276
	LS mean (SE)	-7.5 (0.8)	0.9 (0.8)	-5.1 (0.7)	-2.3 (0.7)
	LS mean difference, 95% CI	-8.4 (-10.5, -6.3)		-2.8 (-4.7, -0.9)	
	P-value (2-sided)	< 0.0001		0.0034	
Other Secondary §					
Number of pulmonary exacerbations through week 52	Number of events	67	90	86	79
	Event rate per year	0.32	0.42	0.29	0.26
	Rate difference, 95% CI	-0.10 (-0.24, 0.04)		0.03 (-0.07, 0.13)	
Absolute change from baseline in CFQ-R RD score through week 24 (points)	n	186	192	268	270
	LS mean (SE)	0.5 (1.1)	-1.7 (1.0)	-1.2 (0.8)	-1.2 (0.8)
	LS mean difference, 95% CI	2.3 (-0.6, 5.2)		-0.1 (-2.3, 2.1)	

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SD: Standard Deviation; SE: Standard Error; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised (respiratory domain); SwCl: Sweat Chloride
Note: Analyses were based on the full analysis set (FAS). FAS was defined as all randomised subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study treatment.
* A 4-week IVA/TEZ/ELX run-in-period was performed to establish an on-treatment baseline.
† The pre-specified non-inferiority margin was -3.0 percentage points.
§ Not controlled for multiplicity.

In Studies 121-102 and 121-103, mean absolute change from baseline in $ppFEV_1$ and absolute change from baseline in sweat chloride through week 24 was maintained through week 52.

Study 121-105

Study 121-105 was an open-label study in people with CF with at least one mutation responsive to IVA/TEZ/ELX. Cohort B1 evaluated the safety, tolerability, and efficacy of D-IVA/TEZ/VNZ in a total of 78 people with CF aged 6 to less than 12 years (mean age 9.1 years (range 6.2 years to 12.0 years), 43.6% female, 56.4% male) during a 24-week treatment period. In Cohort B1, all participants were on IVA/TEZ/ELX at baseline. The mean $ppFEV_1$ at baseline on IVA/TEZ/ELX was 99.7

percentage points (range: 29.3, 146.0), the mean CFQ-R RD score at baseline on IVA/TEZ/ELX was 84.8 (range 16.7, 100), and the mean SwCl at baseline, on IVA/TEZ/ELX, was 40.4 mmol/L (range: 11.5 mmol/L, 109.5 mmol/L).

In study 121-105, Cohort B1, safety and tolerability were the primary endpoints. Efficacy endpoints included absolute change in $ppFEV_1$, absolute change in SwCl, absolute change in CFQ-R respiratory domain score, and number of pulmonary exacerbations (PEx) through week 24.

See Table 6 for a summary of efficacy outcomes.

Table 6: Efficacy analyses, study 121-105 (Cohort B1)

Analysis	Statistic	D-IVA/TEZ/VNZ N = 78
Secondary Efficacy		
Baseline $ppFEV_1$	Mean (SD)	99.7 (15.1)
Baseline SwCl	Mean (SD)	40.4 (20.9)
Absolute change in $ppFEV_1$ from baseline through week 24 (percentage points)	LS mean (95% CI)	0.0 (-2.0, 1.9)
Absolute change in SwCl from baseline through week 24 (mmol/L)	LS mean (95% CI)	-8.6 (-11.0, -6.3)
Absolute change in CFQ-R Respiratory Domain score from baseline through week 24 (points)	LS mean (95% CI)	3.9 (1.5, 6.3)
Number of pulmonary exacerbations through week 24	Event rate per year	0.15

CI: Confidence Interval; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; SD: Standard Deviation; CFQ-R: Cystic Fibrosis Questionnaire-Revised

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with D-IVA/TEZ/VNZ 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 VNZ, TEZ and D-IVA are similar between healthy adult subjects and people with CF. Following initiation of once-daily dosing of D-IVA/TEZ/VNZ plasma concentrations reach steady state within 20 days for VNZ, within 8 days for TEZ, and within 8 days for D-IVA.

Upon dosing D-IVA/TEZ/VNZ to steady state, the accumulation ratio based on AUC is approximately 6.09 for VNZ, 1.92 for TEZ and 1.74 for D-IVA. Key pharmacokinetic parameters for D-IVA/TEZ/VNZ at steady state in people with CF aged 12 years and older are shown in Table 7.

Table 7: Mean (SD) pharmacokinetic parameters of VNZ, TEZ and D-IVA at steady state in people with CF aged 12 years and older			
Dose	**Active Substance**	**C_{max} (mcg/mL)**	**AUC_{0-24h} (mcg·h/mL)**
D-IVA 250 mg /TEZ 100 mg /VNZ 20 mg	VNZ	0.812 (0.344)	18.6 (8.08)
	TEZ	6.77 (1.24)	89.5 (28.0)
	D-IVA	2.33 (0.637)	39.0 (15.3)
SD: Standard Deviation; C_{max}: maximum observed concentration; AUC_{0-24h}: Area Under the Concentration versus time curve at steady state.			

Absorption

VNZ, TEZ, and D-IVA are absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 7.80 hours (3.70 to 11.9 hours), 1.60 hours (1.40 to 1.70 hours), and 3.7 hours (2.7 to 11.4 hours), respectively.

VNZ exposure (AUC) increases approximately 4- to 6-fold when administered with fat-containing meals relative to fasted conditions. D-IVA exposure increases approximately 3- to 4-fold when administered with fat-containing meals relative to fasted conditions, while food has no clinically significant effect on the exposure of TEZ (see section 4.2).

Distribution

VNZ and D-IVA are > 99% bound to plasma protein primarily to albumin and alpha 1-acid glycoprotein. TEZ is approximately 99% bound to plasma proteins, primarily to albumin.

After oral administration of D-IVA/TEZ/VNZ, the mean (SD) apparent volume of distribution of VNZ, TEZ and D-IVA was 90.4 L (31.3), 123 L (43.2) and 157 L (47.3), respectively. VNZ, TEZ and D-IVA do not partition preferentially into human red blood cells.

Biotransformation

VNZ is metabolized extensively in humans, mainly by CYP3A4/5. VNZ has no major circulating metabolites.

TEZ is metabolized 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.

D-IVA is primarily metabolized by CYP3A4/5 to form the two major circulating metabolites, M1-D-IVA and M6-D-IVA. M1-D-IVA has approximately one-fifth the potency of D-IVA and is considered pharmacologically active. M6-D-IVA is not considered pharmacologically active.

Elimination

After oral administration of D-IVA/TEZ/VNZ, the mean (SD) apparent clearance values of VNZ, TEZ and D-IVA were 1.18 (0.455) L/h, 0.937 (0.338) L/h and 6.52 (2.77) L/h, respectively. The mean (SD) terminal half-lives of VNZ, TEZ and D-IVA following administration of the D-IVA/TEZ/VNZ fixed-dose combination tablets are approximately 54.0 (10.1) hours, 92.4 (23.1) hours and 17.3 (2.67) hours, respectively. Based on population pharmacokinetic analysis, the mean (SD) effective half-lives of VNZ, TEZ and D-IVA following administration of the D-IVA/TEZ/VNZ fixed-dose

combination tablets in people with CF are approximately 92.8 (30.2) hours, 22.5 (5.85) hours and 19.2 (8.71) hours, respectively.

Excretion

Following oral administration of ^{14}C-VNZ alone, the majority of radioactivity (91.6%) was eliminated in 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.

Preclinical data indicate that the majority of ^{14}C-D-IVA is excreted in the faeces. Major excreted metabolites of D-IVA were M1-D-IVA and M6-D-IVA. The excretion of D-IVA in humans is expected to be similar to that of IVA, based on similar structure (deuterated isotopologue) and non-clinical data.

After oral administration of ^{14}C-IVA alone, the majority of IVA (87.8%) was eliminated in faeces after metabolic conversion. There was minimal elimination of IVA and its metabolites in urine (only 6.6% of IVA was recovered in the urine).

Hepatic impairment

D-IVA/TEZ/VNZ has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C). Following a single dose of D-IVA/TEZ/VNZ, subjects with moderate hepatic impairment had an approximately 30% lower total VNZ exposures, comparable total TEZ exposures, and 20% lower total D-IVA exposures compared to healthy subjects matched for demographics.

Renal impairment

Urinary excretion of VNZ, TEZ, and D-IVA is negligible (see Elimination).

VNZ alone or in combination with TEZ and D-IVA has not been studied in people with CF with severe renal impairment (eGFR less than 30 mL/min) or in people with CF with end-stage renal disease. Based on population pharmacokinetic (PK) analysis, VNZ exposures appear similar in patients with mild (N = 126; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 2; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 580; eGFR 90 mL/min/1.73 m^2 or greater).

Based on population PK analysis, exposure of TEZ was similar in patients with mild renal impairment (N = 172; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 8; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 637; eGFR 90 mL/min/1.73 m^2 or greater).

Based on population PK analysis, exposure of D-IVA was similar in patients with mild (N = 132; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 2; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 577; eGFR 90 mL/min/1.73 m^2 or greater) (see section 4.2).

Race

Race had no clinically meaningful effect on VNZ exposure based on population PK analysis in whites (N = 664) and non-whites (N = 44). The non-white races consisted of 9 Black or African Americans, 7 Asians, 7 with multiple racial background, 2 American Indian or Alaska Native, 2 with other ethnic background, and 17 not collected.

Very limited population 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 D-IVA in whites (N = 670) and non-whites (N = 41) based on a population PK analysis. The non-white races consisted of 18 Black or African Americans, 2 Asians, 3 with multiple racial background, 1 with other ethnic background, and 17 not collected.

Gender

Based on population PK analysis, there are no clinically relevant differences in exposures of VNZ (433 males compared to 275 females), TEZ, and D-IVA between males and females.

Elderly

Clinical studies of D-IVA/TEZ/VNZ included 2 people with CF aged 65 years and older. This number is not sufficient to determine whether they respond differently from younger people with CF (see sections 4.2 and 4.4).

Paediatric people with CF 6 to less than 18 years of age

VNZ, TEZ, and D-IVA exposures observed in phase 3 studies as determined using population PK analysis are presented by age group in Table 8. VNZ, TEZ, and D-IVA exposures in the 6 to less than 18 years of age are within the range observed in adults with CF.

Table 8: Mean (SD) vanzacaftor, tezacaftor and deutivacaftor exposures by age group

Age group	Weight	Dose	VNZ $AUC_{0\text{-}24h}$ (mcg·h/mL)	TEZ $AUC_{0\text{-}24h}$ (mcg·h/mL)	M1-TEZ $AUC_{0\text{-}24h,\ ss}$ (µg·h/mL)	D-IVA $AUC_{0\text{-}24h}$ (mcg·h/mL)
6 to < 12 years	< 40 kg (N = 70)	VNZ 12 mg qd/ TEZ 60 mg qd/ D-IVA 150 mg qd	13.0 (4.90)	69.1 (20.7)	163 (42.2)	30.2 (11.6)
	≥ 40 kg (N = 8)	VNZ 20 mg qd/ TEZ 100 mg qd/ D-IVA 250 mg qd	18.6 (7.49)	101 (33.7)	162 (51.5)	48.5 (18.7)
12 to < 18 years	- (N = 66)	VNZ 20 mg qd/ TEZ 100 mg qd/ D-IVA 250 mg qd	15.8 (6.52)	93.0 (32.5)	149 (41.2)	37.1 (15.3)
≥ 18 years	- (N = 414)		19.0 (8.22)	89.0 (27.2)	130 (35.2)	39.3 (15.3)

SD: Standard Deviation; $AUC_{0\text{-}24h}$: Area Under the Concentration versus time curve at steady state; qd: once daily.

5.3 Preclinical safety data

Vanzacaftor

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

VNZ was not teratogenic in rats at 10 mg/kg/day and at 40 mg/kg/day in rabbits (approximately 30 and 22 times, respectively, the MRHD based on AUCs of VNZ).

VNZ had no effects on fertility and early embryonic development in rats at oral doses up to 12.5 mg/kg/day in males and 10 mg/kg/day for females (approximately 19 times for males and 30 times for females the MRHD based on AUC of vanzacaftor). Placental transfer of VNZ 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, 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 6 years of age and older, for whom P-glycoprotein expression levels are equivalent to levels observed in adults.

Fertility and pregnancy

TEZ had no effects on fertility and early embryonic development in rats at oral doses up to 200 mg/kg/day in males and 100 mg/kg/day for females (approximately 3 times for males and 3 times for females the MRHD based on AUC of tezacaftor).

Deutivacaftor

D-IVA is a deuterated isotopologue of IVA, with a bridge between their toxicity profiles established through a 13-week rat toxicity study. No additional toxicity studies were conducted for D-IVA, as toxicity data from IVA studies are considered sufficient to demonstrate the toxicity profile of D-IVA.

As for IVA, 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 (IVA)

The NOAEL for fertility findings was 100 mg/kg/day (8 times the MRHD based on summed AUCs of IVA and its metabolites) in male rats and 100 mg/kg/day (5 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 5 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

Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through 35 with IVA dose levels of 10 mg/kg/day and higher (0.3 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 17, in rat pups exposed to IVA to a certain extent through milk ingestion

up to postnatal day 20, in 7-week-old rats, or 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).

Deutivacaftor/tezacaftor/vanzacaftor

Combination repeat-dose toxicity studies in rats involving the co-administration of VNZ, TEZ and D-IVA to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

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

Tablet film coat

Carmine (E120)
Brilliant Blue FCF aluminium lake (E133)
Hydroxypropyl cellulose (E463)
Hypromellose (E464)
Iron oxide red (E172)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Alyftrek 50 mg/20 mg/4 mg film-coated tablets

3 years

Alyftrek 125 mg/50 mg/10 mg film-coated tablets

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Pack sizes

Deutivacaftor 125 mg/tezacaftor 50 mg/vanzacaftor 10 mg film-coated tablets

Alyftrek Pack size of 56 tablets (4 blister foils, each with 14 tablets)

Deutivacaftor 50 mg/tezacaftor 20 mg/vanzacaftor 4 mg film-coated tablets

Alyftrek Pack size of 84 tablets (4 blister foils, each with 21 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

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1943/001
EU/1/25/1943/002

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 30 June 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/en.