SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 as a fixed-dose combination.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

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 is indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see section 5.1, Table 4).

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 *F508del* mutation or another responsive mutation (see section 5.1).

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

Posology

Adults and 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 to < 12 years	< 40 kg	Three tablets of deutivacaftor 50 mg/tezacaftor 20 mg/vanzacaftor 4 mg (total dose of deutivacaftor 150 mg/tezacaftor 60 mg/vanzacaftor 12 mg)
6 to < 12 years	≥ 40 kg	Two tablets of deutivacaftor 125 mg/ tezacaftor 50 mg/ vanzacaftor 10 mg (total dose of deutivacaftor 250 mg/tezacaftor 100 mg/vanzacaftor 20 mg)
≥ 12 years	Any weight	

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) 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).

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

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

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors

6 to < 12 years	< 40 kg	Two tablets of deutivacaftor 50 mg/ tezacaftor 20 mg/vanzacaftor 4 mg every other day (total dose of deutivacaftor 100 mg/tezacaftor 40 mg/vanzacaftor 8 mg)	Two tablets of deutivacaftor 50 mg/ tezacaftor 20 mg/ vanzacaftor 4 mg once a week (total dose of deutivacaftor 100 mg/tezacaftor 40 mg/vanzacaftor 8 mg)
6 to < 12 years	≥ 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
≥ 12 years	Any weight		

Special populations

Elderly population

Clinical studies of Alyftrek did not include a sufficient number of people with CF aged 65 years and older to determine whether they respond differently from younger people with CF.

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. Alyftrek should only be considered when there is a clear medical need, and the benefit exceeds 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. Alyftrek has not been studied in people with CF with severe hepatic impairment (see section 5.2).

Renal impairment

No dose adjustment is recommended for people with CF who have mild or moderate renal impairment. Caution is recommended for people with CF who have severe renal impairment or end-stage renal disease (see section 5.2).

Paediatric population

The safety and efficacy of Alyftrek in children aged less than 6 years have not yet been established. No data are available.

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.

Alyftrek 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 with Alyftrek (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

Elevated transaminases are common in people with CF and have been observed in some people with CF treated with Alyftrek. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all people with CF prior to initiating Alyftrek, 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.

In the event of ALT or AST > 5 × the upper limit of normal (ULN), or ALT or AST > 3 × ULN with bilirubin > 2 × ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve.

Following resolution, consider the benefits and risks of resuming treatment (see sections 4.2, 4.8, and 5.2).

Alyftrek should be used with caution in people with CF with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used, they should be closely monitored after the initiation of treatment (see sections 4.2, 4.8, and 5.2).

Interactions with medicinal products

CYP3A inducers

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

CYP3A inhibitors

Exposures to VNZ, TEZ and D-IVA are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose of Alyftrek 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 Alyftrek (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 Alyftrek

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 Alyftrek efficacy. Co-administration of Alyftrek 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 Alyftrek 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 Alyftrek 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 Alyftrek 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 with Alyftrek (see section 4.2).

Ciprofloxacin

Alyftrek 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 Alyftrek with ciprofloxacin.

Potential for interaction with transporters

In vitro studies showed that VNZ is not a substrate of Breast Cancer Resistance Protein (BCRP), the efflux transporters P-gp, and OATP1B1 or OATP1B3. Exposure to VNZ is not expected to be affected by inhibitors of BCRP, P-gp, and OATP1B1/3.

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 D-IVA/TEZ/VNZ.

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

<u>Medicinal products affected by VNZ, TEZ, and D-IVA</u>

CYP2C9 substrates

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

Potential for interaction with transporters

Alyftrek 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 Alyftrek 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 Alyftrek 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

Alyftrek is not expected to have an impact on the efficacy of oral contraceptives. Alyftrek 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 based on *in vitro* data.

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) in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Because animal reproduction studies are not always predictive of human response, Alyftrek should be used during pregnancy only if the potential benefits outweigh the potential risks.

Breast-feeding

VNZ and TEZ are excreted into the milk of lactating female rats. The effect of D-IVA has not been evaluated; however, IVA is excreted into the milk of lactating female rats. Exposure in rats of ^{14}C-VNZ, ^{14}C-TEZ and ^{14}C-IVA in milk was approximately 0.2, 3.0, and 1.5 times, respectively, the value observed in plasma (based on AUC).

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. VNZ and TEZ had no effects on fertility and reproductive performance indices in male and female rats at doses up to 12.5 mg/kg/day for males (19 times Maximum recommended human dose (MRHD)) and 10 mg/kg/day for females (30 times MRHD) for VNZ and 200 mg/kg/day for males (3 times MRHD) and 100 mg/kg/day for females (3 times MRHD) for TEZ. The effects of D-IVA on fertility have not been evaluated; however, IVA 200 mg/kg/day (13 and 15 times MRHD for females and males, respectively) had an effect on fertility in female and male rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Alyftrek has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Alyftrek is based on data from 480 participants aged 12 years and older in two randomized, ivacaftor/tezacaftor/elexacaftor (IVA/TEZ/ELX)-controlled phase 3 studies (studies 121-102 and 121-103) with 52 weeks of treatment duration. In both studies, all subjects participated in a 4-week run-in period with IVA/TEZ/ELX. In studies 121-102 and 121-103, the proportion of people with CF who discontinued Alyftrek prematurely due to adverse events was 3.8%.

Serious adverse drug reactions that occurred with Alyftrek in 2 or more participants (≥ 0.4%) were ALT increased (0.4%) and AST increased (0.4%). The most common (≥ 10%) adverse drug reactions in people with CF treated with Alyftrek were headache (15.8%) and diarrhoea (12.1%).

Tabulated list of adverse reactions

Table 3 shows overall incidence of adverse drug reactions of people with CF treated with Alyftrek. Adverse drug reactions for Alyftrek 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 reactions by preferred term, frequency		
System Organ Class (SOC)	**Adverse Drug Reactions (Preferred Term)**	**Frequency for Alyftrek**
Nervous system disorders	Headache	very common
Gastrointestinal disorders	Diarrhoea	very common
Hepatobiliary disorders	Alanine aminotransferase increased	common
	Aspartate aminotransferase increased	common
Skin and subcutaneous tissue disorders	Rash	common
Investigations	Blood creatine phosphokinase increased	common

Safety data from the following studies were generally consistent with the safety data observed in studies 121-102 and 121-103:

- A 24-week, open-label study (study 121-105, Cohort B1) in 78 people with CF aged 6 to less than 12 years.

Detailed 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 Alyftrek. The incidence of adverse reactions of transaminase elevations was 9.0% with Alyftrek. Of the Alyftrek-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 Alyftrek. 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.

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

Increased creatine phosphokinase

In studies 121-102 and 121-103, the incidence of maximum creatine phosphokinase > 5 × the ULN was 7.9% with Alyftrek. Of the Alyftrek-treated participants, 0.2% discontinued treatment for increased creatine phosphokinase.

Paediatric population

The safety data of Alyftrek in study 121-105, Cohort B1 was evaluated in 78 people with CF aged 6 to less than 12 years. The safety profile is generally consistent among adolescents and adult patients.

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).

Other special populations

The safety profile of Alyftrek was generally similar across all subgroups of patients, including analysis by age, sex, 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 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 of clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

Clinical outcomes were consistent with *in vitro* results and indicate that a single responsive allele (including the *F508del* mutation) is sufficient to result in a significant clinical response.

Table 4 lists responsive *CFTR* mutations based on clinical and/or *in vitro* data.

Table 4: List of *CFTR* gene mutations that are responsive to Alyftrek

1140-1151dup	A561E	F1052V	G628A	K522Q	P1021T	R516G	T1057R
1341G→A	A566D	F1074L	G628R	K951E	P111L	R516S	T1086A
1461ins GAT	A613T	F1078S	G85E	L1011S	P1372T	R553Q	T1086I
1507_1515del9	A62P	F1099L	G85V	L102R	P140S	R555G	T1246I
1898+3A→G	A72D	F1107L	G91R	L102R;F1016S*	P205S	R560S	T1299I
2055del9	A872E	F191V	G930E	L1065P	P439S	R560T	T1299K
2183A→G	c.1367_1369dupTTG	F200I	G970D	L1065R	P499A	R600S	T164P
2752-26A→G	C225R	F311del	G970S	L1077P	P574H	R668C	T338I
2789+2insA	C491R	F311L	G970V	L1227S	P5L	R709Q	T351I
2789+5G→A	C590Y	F312del	H1054D	L1324P	P67L	R74Q	T351S
2851A/G	C866Y	F433L	H1079P	L1335P	P750L	R74Q;R297Q*	T351S;R851L*
293A→G	D110E	F508C	H1085P	L137P	P798S	R74Q;V201M;D1270N*	T388M
296+28A→G	D110H	F508C;S1251N*	H1085R	L137R	P988R	R74W	T465I
3007del6	D110N	F508del	H1375N	L1388P	P99L	R74W;D1270N*	T465N

3041-15T→G	D1152A	F508del; R1438W*	H1375P	L1480P	Q1012P	R74W;R1070W; D1270N*	T501A
3131del15	D1152H	F575Y	H139L	L159S	Q1100P	R74W;S945L*	T582S
3132T→G	D1270N	F587I	H139R	L15P	Q1209P	R74W;V201M*	T604I
3141del9	D1270Y	F587L	H146R	L15P;L1253F*	Q1291H	R74W;V201M;D1270N*	T908N
3143del9	D1312G	F693L(TTG)	H147del	L165S	Q1291R	R74W;V201M;L997F*	T990I
314del9	D1377H	F87L	H147P	L167R	Q1313K	R751L	V1008D
3195del6	D1445N	F932S	H199Q	L206W	Q1352H	R75L	V1010D
3199del6	D192G	G1047D	H199R	L210P	Q151K	R75Q	V1153E
3272-26A→G	D192N	G1047R	H199Y	L293P	Q179K	R75Q;L1065P*	V11I
3331del6	D373N	G1061R	H609L	L320V	Q237E	R75Q;N1088D*	V1240G
3410T→C	D426N	G1069R	H609R	L327P	Q237H	R75Q;S549N*	V1293G
3523A→G	D443Y	G1123R	H620P	L32P	Q237P	R792G	V1293I
3600G→A	D443Y; G576A; R668C*	G1173S	H620Q	L333F	Q30P	R792Q	V1415F
3601A→C	D513G	G1237V	H939R	L333H	Q359K/T360K*	R810G	V201M
3761T→G	D529G	G1244E	H939R; H949L*	L346P	Q359R	R851L	V232A
3791C/T	D565G	G1244R	H954P	L441P	Q372H	R933G	V232D
3849+10kbC→T	D567N	G1247R	I1023R	L453S	Q452P	S1045Y	V317A
3849+40A→G	D572N	G1249E	I1027T	L467F	Q493L	S108F	V322M
3849+4A→G	D579G	G1249R	I105N	L558F	Q493R	S1118F	V392G
3850-3T→G	D58H	G1265V	I1139V	L594P	Q552P	S1159F	V456A
3850G→A	D58V	G126D	I1203V	L610S	Q98P	S1159P	V456F
3978G→	D614G	G1298V	I1234L	L619S	Q98R	S1188L	V520F

C							
4005+2T→C	D651H	G1349D	I1234Vdel6aa	L633P	R1048G	S1235R	V520I
4193T→G	D651N	G149R	I125T	L636P	R1066C	S1251N	V562I
546insCTA	D806G	G149R; G576A; R668C*	I1269N	L88S	R1066G	S1255P	V562I;A1006E*
548insTAC	D836Y	G178E	I1366N	L927P	R1066H	S13F	V562L
5T;TG12	D924N	G178R	I1366T	L967F;L1096R*	R1066L	S13P	V591A
5T;TG13	D979A	G194R	I1398S	L967S	R1066M	S158N	V603F
621+3A→G	D979V	G194V	I148L	L973F	R1070P	S182R	V754M
711+3A→G	D985H	G213E	I148N	L997F	R1070Q	S18I	V920L
A1006E	D985Y	G213E;R668C*	I148T	M1101K	R1070W	S18N	V920M
A1025D	D993A	G213V	I148T;H609R*	M1101R	R1162L	S308P	V93D
A1067P	D993G	G226R	I175V	M1137R	R1162Q	S341P	W1098C
A1067T	D993Y	G239R	I331N	M1137V	R117C	S364P	W1282G
A1067V	E1104K	G253R	I336K	M1210K	R117C;G576A;R668C*	S434P	W1282R
A107G	E1104V	G27E	I336L	M150K	R117G	S492F	W202C
A1081V	E1126K	G27R	I444S	M150R	R117H	S50P	W361R
A1087P	E116K	G314E	I497S	M152L	R117L	S519G	W496R
A120T	E116Q	G314R	I502T	M152V	R117L;L997F*	S531P	Y1014C
A1319E	E1221V	G424S	I506L	M265R	R117P	S549I	Y1032C
A1374D	E1228K	G437D	I506T	M348K	R1239S	S549N	Y1032N
A141D	E1409K	G451V	I506V	M394L	R1283G	S549R	Y1073C
A1466S	E1433K	G461R	I506V;D1168G*	M469V	R1283M	S557F	Y1092H
A155P	E193K	G461V	I521S	M498I	R1283S	S589I	Y109C
A234D	E217G	G463V	I530N	M952I	R1438W	S589N	Y109H
A234V	E264V	G480C	I556V	M952T	R170H	S624R	Y109N
A238V	E282D	G480D	I586V	M961L	R248K	S686Y	Y122C
A309D	E292K	G480S	I601F	N1088D	R258G	S737F	Y1381H

A349V	E384K	G500D	I601T	N1195T	R297Q	S821G	Y161C
A357T	E403D	G545R	I618N	N1303I	R31C	S898R	Y161D
A455E	E474K	G551A	I618T	N1303K	R31L	S912L	Y161S
A455V	E527G	G551D	I807M	N186K	R334L	S912L;G1244V*	Y301C
A457T	E56K	G551R	I86M	N187K	R334Q	S912T	Y517C
A462P	E588V	G551S	I980K	N396Y	R334W	S945L	Y563N
A46D	E60K	G576A	K1060T	N418S	R347H	S955P	Y569C
A534E	E822K	G576A; R668C*	K162E	N900K	R347L	S977F	Y89C
A554E	E831X	G576A;S1359Y*	K464E	P1013H	R347P	S977F;R1438W*	Y913C
A559T	E92K	G622D	K464N	P1013L	R352Q	T1036N	Y913S
A559V	F1016S	G622V	K522E	P1021L	R352W	T1053I	Y919C

* 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.

Pharmacodynamic effects

Effects on sweat chloride

In study 121-102 (people with CF heterozygous for a *F508del* and a *CFTR* mutation that results in a protein that is not responsive to IVA or TEZ/IVA [minimal function mutation]) the treatment difference of Alyftrek 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 Alyftrek 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 Alyftrek in people with CF aged 12 years and older was evaluated in two, phase 3, randomized, double-blind, IVA/TEZ/ELX-controlled studies (studies 121-102 and 121-103). The pharmacokinetic profile, safety, and efficacy of Alyftrek in people with CF aged 6 to less than 12 years are supported with evidence from studies of Alyftrek 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, randomized, double-blind, IVA/TEZ/ELX-controlled study in people with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to IVA or TEZ/IVA (minimal function mutation). A total of 398 people with CF aged 12 years and older (mean age 30.8 years) received IVA/TEZ/ELX during a 4-week run-in period and were then randomized to receive Alyftrek or IVA/TEZ/ELX during the 52-week treatment period. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 67.1 percentage points (range: 28.0, 108.6) 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, randomized, 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 (mean age 33.7 years) received IVA/TEZ/ELX during a 4-week run-in period and were then randomized to receive Alyftrek or IVA/TEZ/ELX during the 52-week treatment period. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 66.8 percentage points (range: 36.4, 112.5) 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. Key secondary endpoints evaluated superiority in mean absolute change from baseline in SwCl through week 24, and the proportion of participants achieving SwCl < 60 mmol/L and SwCl < 30 mmol/L through week 24.

In study 121-102, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (1-sided $P < 0.0001$ for non-inferiority; 95% CI: -0.7, 1.1) in absolute change in $ppFEV_1$ from baseline through week 24 compared to IVA/TEZ/ELX. In study 121-103, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (1-sided $P < 0.0001$ for non-inferiority; 95% CI: -0.5, 0.9) in absolute change in $ppFEV_1$ from baseline through week 24 compared to IVA/TEZ/ELX. In studies 121-102 and 121-103, mean absolute change from baseline in $ppFEV_1$ through week 24 was maintained through week 52.

As the lower bounds of the 95% CI of the LS mean difference in absolute change in $ppFEV_1$ from baseline through week 24 was greater than -3.0 percentage points (the pre-specified non-inferiority margin) in study 121-102 and study 121-103, these results demonstrate non-inferiority of Alyftrek compared to IVA/TEZ/ELX.

In studies 121-102 and 121-103, Alyftrek was superior to IVA/TEZ/ELX on all key secondary endpoints. On the first key secondary endpoint, when compared to IVA/TEZ/ELX, treatment with Alyftrek resulted in a reduction of -8.4 mmol/L (95% CI: -10.5, -6.3; $P < 0.0001$) and -2.8 mmol/L (95% CI: -4.7, -0.9; $P = 0.0034$) in SwCl through week 24, in studies 121-102 and 121-103, respectively. Absolute change from baseline in SwCl through week 24 was maintained through week 52 in both trials. On the remaining key secondary endpoints, treatment with Alyftrek resulted in 86% of people with CF achieving a SwCl level below 60 mmol/L through week 24, compared to 77% of people treated with IVA/TEZ/ELX (odds ratio 2.21; 95% CI: 1.55, 3.15; $P < 0.0001$), and 31% of people with CF achieving a

SwCl level below 30 mmol/L through week 24, compared to 23% of people treated with IVA/TEZ/ELX (odds ratio 2.87; 95% CI: 2.00, 4.12; $P < 0.0001$).

Other secondary endpoints (pulmonary exacerbation rate, change in CFQ-R RD score from baseline) demonstrated consistent benefit between Alyftrek and IVA/TEZ/ELX.

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**	
		Alyftrek N = 196	**IVA/TEZ/ELX N = 202**	**Alyftrek 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	
Proportion of participants with SwCl < 60 mmol/L† through week 24	n	**465 Alyftrek vs 479 IVA/TEZ/ELX**			
	Proportion (%)	86 Alyftrek vs 77 IVA/TEZ/ELX			
	Odds Ratio, 95% CI¶	2.21 (1.55, 3.15)			
	P-value (2-sided)	< 0.0001			
Proportion of participants with SwCl < 30 mmol/L§ through week 24	n	**465 Alyftrek vs 479 IVA/TEZ/ELX**			
	Proportion (%)	31 Alyftrek vs 23 IVA/TEZ/ELX			
	Odds Ratio, 95% CI¶	2.87 (2.00, 4.12)			
	P-value (2-sided)	< 0.0001			
Other Secondary**					
Number of pulmonary exacerbations through week	Number of events	67	90	86	79
	Event rate per year	0.32	0.42	0.29	0.26
	Rate difference,	-0.10 (-0.24, 0.04)		0.03 (-0.07, 0.13)	

Table 5: Efficacy analyses from study 121-102 and study 121-103					
Analysis*	**Statistic**	**Study 121-102**		**Study 121-103**	
		Alyftrek N = 196	**IVA/TEZ/ELX N = 202**	**Alyftrek N = 284**	**IVA/TEZ/ELX N = 289**
52	95% CI				
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; 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) unless otherwise noted. FAS was defined as all randomized subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug.
* A 4-week IVA/TEZ/ELX run-in-period was performed to establish an on-treatment baseline.
† SwCl ≥ 60 mmol/L meets the diagnostic threshold for CF as evidence of CFTR dysfunction.
§ Normal SwCl levels are considered < 30 mmol/L.
¶ Odds ratio > 1 favours Alyftrek.
# The pre-specified non-inferiority margin was -3.0 percentage points.
** Not controlled for multiplicity.

Study 121-105

Study 121-105 was multicohort, open-label study in people with CF with at least one mutation responsive to IVA/TEZ/ELX. Cohort A1 evaluated pharmacokinetic and safety parameters of Alyftrek during a 22-day treatment period in a total of 17 people with CF aged 6 to less than 12 years of age. Cohort B1 evaluated the safety, tolerability, and efficacy of Alyftrek in a total of 78 people with CF aged 6 to less than 12 years (mean age 9.1 years) 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) 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, proportion of participants with SwCl of < 60 mmol/L, proportion of participants with SwCl of < 30 mmol/L, absolute change in CFQ-R respiratory domain score, and number of 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)
Proportion of participants with SwCl <60 mmol/L[*] through week 24	Proportion (95% CI)	95% (87%, 99%)
Proportion of participants with SwCl <30 mmol/L[†] through week 24	Proportion (95% CI)	53% (41%, 64%)
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; CFQ-R: Cystic Fibrosis Questionnaire-Revised

[*] SwCl ≥ 60 mmol/L meets the diagnostic threshold for CF as evidence of CFTR dysfunction.

[†] Normal SwCl levels are considered < 30 mmol/L.

The Medicines and Healthcare products Regulatory Agency (MHRA) has deferred the obligation to submit the results of studies with Alyftrek 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)***	**$AUC_{0\text{-}24h}$, (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; $AUC_{0\text{-}24h}$: Area Under the Concentration versus time curve at steady state. *Values based on population PK modelling.			

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. Relative to IVA, D-IVA exhibited more metabolic stability and formed less M1-D-IVA, the deuterated-equivalent of M1-IVA. M1-D-IVA has approximately one-fifth the potency of D-IVA and is considered pharmacologically active. M6-D-IVA is the other major metabolite of D-IVA, the deuterated-equivalent of M6-IVA, and 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. The mean (SD) effective half-lives of VNZ, TEZ and D-IVA following administration of the D-IVA/TEZ/VNZ fixed-dose combination tablets 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 (91.6%), the majority of radioactivity 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 and ^{14}C-IVA are excreted in the faeces. Major excreted metabolites of D-IVA were M1-D-IVA and M6-D-IVA and major excreted metabolites for IVA were M1-IVA and M6-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 were 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 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, TEZ, and D-IVA between males and females.

Elderly

Clinical studies of D-IVA/TEZ/VNZ did not include a sufficient number of people with CF aged 65 years and older to determine whether they respond differently from younger people with CF (see section 4.2).

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_{0-24h} (mcg·h/mL)**	**TEZ AUC_{0-24h} (mcg·h/mL)**	**D-IVA AUC_{0-24h} (mcg·h/mL)**
6 to < 12 years	< 40 kg (N = 70)	VNZ 12 mg qd/ TEZ 60 mg qd/ D-IVA150 mg qd	13.0 (4.90)	69.1 (20.7)	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)	48.5 (18.7)

Table 8: Mean (SD) vanzacaftor, tezacaftor and deutivacaftor Exposures by Age Group					
Age group	**Weight**	**Dose**	**VNZ AUC_{0-24h} (mcg·h/mL)**	**TEZ AUC_{0-24h} (mcg·h/mL)**	**D-IVA AUC_{0-24h} (mcg·h/mL)**
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)	37.1 (15.3)
≥ 18 years	- (N = 414)		19.0 (8.22)	89.0 (27.2)	39.3 (15.3)
SD: Standard Deviation; AUC_{0-24h}: Area Under the Concentration versus time curve at steady state; qd: once daily.					

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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 male or 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.

Deutivacaftor

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

D-IVA is a deuterated isotopologue of IVA with an established toxicity profile similar to IVA based on a 13-week single-agent repeat dose toxicity study; therefore, reproductive and developmental toxicity data and carcinogenicity data from IVA are expected to be equivalent to D-IVA.

Fertility and Pregnancy

The effect of D-IVA on fertility and pregnancy has not been evaluated; however, IVA was associated with a reduction in overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the estrous cycle in females at 200 mg/kg/day dose (approximately 13 times the MRHD based on AUC of IVA). Slight decreases of the seminal vesicle weights were observed in males at 200 mg/kg/day dose (approximately 15 times the MRHD based on AUC of IVA).

In a pre- and post-natal development study in pregnant rats at doses above 100 mg/kg/day (approximately 8 times the MRHD), IVA resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights. 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.

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

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 lidding.

Alyftrek Pack size of 56 tablets (4 foil blisters, 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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 22352/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/12/2025