NEW ZEALAND DATA SHEET – ALYFTREK®
(vanzacaftor/tezacaftor/deutivacaftor)
film-coated tablets

1 ALYFTREK FILM-COATED TABLETS

Alyftrek 10/50/125 (vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg) film-coated tablets

Alyftrek 4/20/50 (vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg) film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alyftrek 10/50/125 vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets
Each film-coated tablet contains 10 mg of vanzacaftor (equivalent to 10.6 mg of vanzacaftor calcium dihydrate), 50 mg of tezacaftor and 125 mg of deutivacaftor as a fixed-dose combination.

Alyftrek 4/20/50 vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets
Each film-coated tablet contains 4 mg of vanzacaftor (equivalent to 4.24 mg of vanzacaftor calcium dihydrate), 20 mg of tezacaftor and 50 mg of deutivacaftor as a fixed-dose combination.

For the full list of excipients, see ection 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Film-coated tablets

Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg
Purple, capsule-shaped tablet debossed with “V10” on one side and plain on the other (15 mm × 7 mm).

Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
Purple, round-shaped tablet debossed with “V4” on one side and plain on the other (7.35 mm diameter).

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 PHARMACODYNAMIC PROPERTIES, Table 4).

4.2 DOSE AND METHOD OF ADMINISTRATION

If the patient’s genotype is unknown, use a genotyping assay to confirm the presence of at least one *F508del* mutation or another responsive mutation.

Dosage

Adults and paediatric patients 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 vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
	≥ 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg

Method of Administration

For oral use. Tablets should be swallowed whole.

Alyftrek 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, peanut butter, cheeses, nuts, whole milk, or meats (see section 5.2 PHARMACOKINETIC PROPERTIES).

Food or drink containing grapefruit should be avoided during treatment with Alyftrek (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

Dosage adjustment

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 of Alyftrek should be reduced as recommended in Table 2 (see sections 4.4 SPECIAL WARNINS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 2: Dosing schedule for concomitant use of Alyftrek with moderate or strong CYP3A inhibitors			
Age	**Weight**	**Moderate CYP3A Inhibitors**	**Strong CYP3A Inhibitors**
≥ 6 years	< 40 kg	Two tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg every other day	Two tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg once a week
	≥ 40 kg	One tablet of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg every other day	One tablet of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg once a week

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A). Use not recommended in moderate hepatic impairment (Child-Pugh Class B). Alyftrek should only be considered when there is a clear medical need, and the benefit exceeds the risk. Liver function tests should be closely monitored. Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with Alyftrek (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment. Caution is recommended for patients with severe renal impairment or end-stage renal disease (see section 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

In cases of hypersensitivity to the active substance or to any component of this medication, patients should not be treated with this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

- *Mild Hepatic Impairment (Child-Pugh Class A):* No dose adjustment is recommended. Liver function tests should be closely monitored.
- *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.
- *Severe Hepatic Impairment (Child-Pugh Class C):* Should not be used. Alyftrek has not been studied in patients with severe hepatic impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

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 drug containing elexacaftor, tezacaftor and ivacaftor which contains one active ingredient that is the same (tezacaftor) and one similar (ivacaftor) to Alyftrek. 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.

Interrupt Alyftrek and promptly measure serum transaminases and total bilirubin 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). Interrupt dosing in the event of ALT or AST > 5 × the upper limit of normal (ULN), or ALT or AST > 3 × ULN with total bilirubin > 2 × ULN. Follow laboratory tests closely until the abnormalities resolve. Following the resolution of transaminase elevations consider the benefits and risks of resuming treatment. Patients who resume treatment after interruption should be monitored closely (see sections 4.2 DOSAGE AND METHOD

OF ADMINISTRATION, 4.8 ADVERSE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES).

In people with CF with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension), Alyftrek should be used with caution and only if the benefits are expected to outweigh the risks. If used, they should be closely monitored after the initiation of treatment (4.2 DOSAGE AND METHOD OF ADMINISTRATION, 4.8 ADVERSE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES).

Patients who discontinued or interrupted treatment with a drug containing tezacaftor or ivacaftor due to adverse reactions

There are no available safety data for Alyftrek in patients who previously discontinued or interrupted treatment with a drug containing tezacaftor or ivacaftor due to adverse reactions. Consider the benefits and risks before using Alyftrek in these patients. If Alyftrek is used in these patients, monitor closely as clinically appropriate.

Interactions with medicinal products

CYP3A inducers
Exposures to vanzacaftor, tezacaftor and deutivacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduction of Alyftrek efficacy; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

CYP3A inhibitors
Exposures to vanzacaftor, tezacaftor and deutivacaftor 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 DOSAGE AND METHOD OF ADMINISTRATION and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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-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 ivacaftor cannot be excluded. As deutivacaftor is a deuterated isotopologue of ivacaftor, 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 PRECLINICAL SAFETY DATA).

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 PHARMACOKINETIC PROPERTIES).

Effects on laboratory tests
Refer to section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Elevated transaminases and hepatic injury.

Use in the elderly
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.

Paediatric use
The safety and efficacy of Alyftrek in children aged less than 6 years have not been established (see section 5.1 PHARMACODYNAMIC PROPERTIES).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products affecting the pharmacokinetics of Alyftrek

CYP3A inducers
Vanzacaftor, tezacaftor and deutivacaftor are substrates of CYP3A. Vanzacaftor and deutivacaftor 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Examples of moderate to strong CYP3A inducers include:
- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's Wort (*Hypericum perforatum*), and efavirenz.

CYP3A inhibitors
Co-administration with itraconazole, a strong CYP3A inhibitor, increased vanzacaftor AUC by 10.5-fold, tezacaftor AUC by 4.0- to 4.5-fold and deutivacaftor AUC by 11.1-fold. The dose of Alyftrek should be reduced when co-administered with strong CYP3A inhibitors (see sections 4.2 DOSAGE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 vanzacaftor, tezacaftor, and deutivacaftor 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 DOSAGE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 vanzacaftor, tezacaftor and deutivacaftor. Food or drink containing grapefruit should be avoided during treatment with Alyftrek (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Ciprofloxacin
Vanzacaftor/tezacaftor/deutivacaftor was not evaluated for concomitant use with ciprofloxacin. However, ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor and is not expected to have a clinically relevant effect on the exposure of vanzacaftor or deutivacaftor. Therefore, no dose adjustment is necessary during concomitant administration of Alyftrek with ciprofloxacin.

Medicinal products affected by Alyftrek

CYP2C9 substrates

Deutivacaftor 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.

Breast Cancer Resistance Protein (BCRP) Substrates

Vanzacaftor and deutivacaftor 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.

Potential for interaction with transporters

Alyftrek was not evaluated for concomitant use with P-glycoprotein (P-gp) substrates. However, co-administration of tezacaftor/ivacaftor 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 cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

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

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. Tezacaftor in combination with ivacaftor and ivacaftor alone have been studied with ethinyl estradiol/norethindrone and were found to have no clinically relevant effect on the exposures of the oral contraceptive. Vanzacaftor, tezacaftor, and deutivacaftor have low potential to induce or inhibit CYP3A based on *in vitro* data.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data available on the effect of vanzacaftor, tezacaftor, and deutivacaftor on fertility in humans.

Vanzacaftor and tezacaftor had no effects on fertility and reproductive performance indices in male and female rats at doses up to 12.5 mg/kg/day in males and 10 mg/kg/day for females for vanzacaftor and 200 mg/kg/day for males and 100 mg/kg/day for females for tezacaftor. The effects of deutivacaftor on fertility have not been evaluated; however, ivacaftor had an effect on fertility in male and female rats (see section 5.3 PRECLINICAL SAFETY DATA).

Use in pregnancy

No adequate and well-controlled studies of Alyftrek in pregnant women have been conducted. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3 PRECLINICAL SAFETY DATA). 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.

Use in lactation

Vanzacaftor and tezacaftor are excreted into the milk of lactating female rats. The effect of deutivacaftor has not been evaluated; however, ivacaftor is excreted into the milk of lactating female rats. Exposure in rats of ^{14}C-vanzacaftor, ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 0.2, 3.0, and 1.5 times, respectively, the value observed in plasma (based on AUC). Because it is not known if vanzacaftor, tezacaftor, deutivacaftor, or their metabolites are excreted in human milk, Alyftrek should be used during breastfeeding only if the potential benefits outweigh the potential risks to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Alyftrek is not expected to have an impact 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, elexacaftor/tezacaftor/ivacaftor-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 elexacaftor/tezacaftor/ivacaftor. 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%).

The safety profile of Alyftrek was generally similar across all subgroups of participants, including analysis by age, sex, baseline percent predicted Forced Expiratory Volume in one second ($ppFEV_1$), and geographic regions.

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).

Table 3: Adverse reactions by preferred term, incidence and frequency			
System Organ Class (SOC)	**Adverse Drug Reactions (Preferred Term)**	**Alyftrek N = 480 n (%)**	**Frequency for Alyftrek**
Nervous system disorders	Headache	76 (15.8)	very common
Gastrointestinal disorders	Diarrhoea	58 (12.1)	very common
Skin and subcutaneous tissue disorders	Rash	37 (7.7)	common
Investigations	Blood creatine phosphokinase increased	43 (9.0)	common
	Alanine aminotransferase increased	38 (7.9)	common
	Aspartate aminotransferase increased	33 (6.9)	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 events

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.

Reporting suspected adverse effects
Reporting of suspected adverse reactions after authorisation of the medicine 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 at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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: Respiratory system, Other respiratory system products; ATC code: R07AX32

Mechanism of action

Vanzacaftor and tezacaftor 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. Deutivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of vanzacaftor, tezacaftor and deutivacaftor 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 vanzacaftor/tezacaftor/deutivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Vanzacaftor/tezacaftor/deutivacaftor 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 (see Clinical efficacy).

Table 4 lists responsive *CFTR* mutations based on clinical data and/or *in vitro* data in FRT cells indicating that vanzacaftor/tezacaftor/deutivacaftor increases chloride transport to at least 10% of normal over baseline.

Table 4: List of *CFTR* Gene Mutations that are Responsive to Alyftrek							
1341G→A	*A72D*	*F508C;S1251N**	*H139R*	*L15P*	*Q372H*	*R709Q*	*V1240G*
1507_1515del9	*C491R*	*F508del*	*H199R*	*L165S*	*Q452P*	*R74Q*	*V1293G*

1898+3A→G	*D110E*	*F575Y*	*H199Y*	*L206W*	*Q493R*	*R74W*	*V201M*
2183A->G	*D110H*	*F587I*	*H609R*	*L320V*	*Q552P*	*R74W;D1270N*[*]	*V232D*
2752-26A→G	*D1152H*	*G1047R*	*H620P*	*L333F*	*Q98R*	*R74W;V201M*[*]	*V392G*
2789+2insA	*D1270N*	*G1061R*	*H620Q*	*L333H*	*R1048G*	*R74W;V201M;D1270N*[*]	*V456A*
2789+5G→A	*D1445N*	*G1069R*	*H939R*	*L346P*	*R1066C*	*R751L*	*V456F*
296+28A→G	*D192G*	*G1123R*	*H939R;H949L*	*L441P*	*R1066H*	*R75L*	*V520F*
3041-15T→G	*D443Y*	*G1244E*	*I1027T*	*L453S*	*R1066L*	*R75Q*	*V562I*
3141del9	*D443Y;G576A;R668C*[*]	*G1247R*	*I105N*	*L619S*	*R1066M*	*R792G*	*V603F*
3195del6	*D513G*	*G1249R*	*I1139V*	*L967S*	*R1070Q*	*R933G*	*V754M*
3199del6	*D565G*	*G126D*	*I1234Vdel6aa*	*L997F*	*R1070W*	*S1045Y*	*W1098C*
3272-26A→G	*D579G*	*G1349D*	*I125T*	*M1101K*	*R1162L*	*S108F*	*W1282R*
3600G→A	*D614G*	*G149R*	*I1269N*	*M1101R*	*R117C*	*S1118F*	*W361R*
3849+10kbC→T	*D836Y*	*G178E*	*I1366N*	*M1137V*	*R117C;G576A;R668C*	*S1159F*	*Y1014C*
3849+40A→G	*D924N*	*G178R*	*I1398S*	*M150K*	*R117G*	*S1159P*	*Y1032C*
3849+4A→G	*D979V*	*G194R*	*I148N*	*M152V*	*R117H*	*S1235R*	*Y109N*
3850-3T→G	*D993Y*	*G194V*	*I148T*	*M265R*	*R117L*	*S1251N*	*Y161D*
4005+2T→C	*E116K*	*G27E*	*I175V*	*M952I*	*R117P*	*S1255P*	*Y161S*
546insCTA	*E116Q*	*G27R*	*I331N*	*M952T*	*R1283M*	*S13F*	*Y301C*
5T;TG12	*E193K*	*G314E*	*I336K*	*N1088D*	*R1283S*	*S341P*	*Y563N*
5T;TG13	*E292K*	*G424S*	*I502T*	*N1303I*	*R170H*	*S364P*	*Y569C*
621+3A→G	*E403D*	*G463V*	*I506L*	*N1303K*	*R258G*	*S492F*	*Y913C*
711+3A→G	*E474K*	*G480C*	*I506T*	*N186K*	*R297Q*	*S549I*	
A1006E	*E56K*	*G480S*	*I556V*	*N187K*	*R31C*	*S549N*	
A1067P	*E588V*	*G551A*	*I601F*	*N418S*	*R31L*	*S549R*	
A1067T	*E60K*	*G551D*	*I618T*	*P140S*	*R334L*	*S589N*	
A107G	*E822K*	*G551S*	*I807M*	*P205S*	*R334Q*	*S737F*	
A120T	*E831X*	*G576A*	*I980K*	*P499A*	*R347H*	*S912L*	
A234D	*E92K*	*G576A;R668C*[*]	*K1060T*	*P574H*	*R347L*	*S945L*	
A309D	*F1016S*	*G622D*	*K162E*	*P5L*	*R347P*	*S977F*	
A349V	*F1052V*	*G628R*	*K464E*	*P67L*	*R352Q*	*T1036N*	
A455E	*F1074L*	*G85E*	*L1011S*	*P750L*	*R352W*	*T1053I*	
A46D	*F1099L*	*G91R*	*L102R*	*P99L*	*R516G*	*T1086I*	
A554E	*F1107L*	*G970D*	*L1065P*	*Q1100P*	*R516S*	*T1246I*	
A559T	*F191V*	*G970S*	*L1077P*	*Q1291R*	*R553Q*	*T1299I*	
A559V	*F200I*	*H1054D*	*L1324P*	*Q1313K*	*R555G*	*T338I*	
A561E	*F311del*	*H1085P*	*L1335P*	*Q237E*	*R560S*	*T351I*	
A613T	*F311L*	*H1085R*	*L137P*	*Q237H*	*R560T*	*T604I*	
A62P	*F508C*	*H1375P*	*L1480P*	*Q359R*	*R668C*	*V1153E*	

[*] 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.

Clinical trials

Pharmacodynamic effects

Effects on sweat chloride
In Study 121-102 (people with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor [minimal function mutation]) the treatment difference of Alyftrek compared to elexacaftor/tezacaftor/ivacaftor 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 elexacaftor/tezacaftor/ivacaftor with no *F508del* mutation), the treatment difference of Alyftrek compared to elexacaftor/tezacaftor/ivacaftor 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 elexacaftor/tezacaftor/ivacaftor), 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 vanzacaftor maximum recommended dose, and doses up to 3 times over the tezacaftor and deutivacaftor maximum recommended doses, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Clinical efficacy

The efficacy of Alyftrek in people with CF aged 12 years and older was evaluated in two, Phase 3, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor-controlled studies (Study 121-102 and Study 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, elexacaftor/tezacaftor/ivacaftor-controlled study in people with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function mutation). A total of 398 people with CF aged 12 years and older (mean age 30.8 years) received elexacaftor/tezacaftor/ivacaftor during a 4-week run-in period and were then randomized to receive Alyftrek or elexacaftor/tezacaftor/ivacaftor 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, elexacaftor/tezacaftor/ivacaftor-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 elexacaftor/tezacaftor/ivacaftor with no *F508del* mutation. A total of 573 people with CF aged 12 years and older (mean age 33.7 years) received elexacaftor/tezacaftor/ivacaftor during a 4-week run-in period and were then randomized to receive Alyftrek or elexacaftor/tezacaftor/ivacaftor 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 elexacaftor/tezacaftor/ivacaftor. 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 elexacaftor/tezacaftor/ivacaftor. 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 elexacaftor/tezacaftor/ivacaftor.

In Studies 121-102 and 121-103, Alyftrek was superior to elexacaftor/tezacaftor/ivacaftor on all key secondary endpoints. On the first key secondary endpoint, when compared to elexacaftor/tezacaftor/ivacaftor, 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 elexacaftor/tezacaftor/ivacaftor (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 elexacaftor/tezacaftor/ivacaftor (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 elexacaftor/tezacaftor/ivacaftor.

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	**Elexacaftor/tezacaftor/ivacaftor N = 202**	**Alyftrek N = 284**	**Elexacaftor/tezacaftor/ivacaftor N = 289**
Primary					
Baseline $ppFEV_1$	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	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 elexacaftor/tezacaftor/ivacaftor**	
	Proportion (%)	86 Alyftrek	vs	77 elexacaftor/tezacaftor/ivacaftor	
	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 elexacaftor/tezacaftor/ivacaftor**	
	Proportion (%)	31 Alyftrek	vs	23 elexacaftor/tezacaftor/ivacaftor	
	Odds Ratio, 95% CI¶	2.87 (2.00, 4.12)			
	P-value (2-sided)	< 0.0001			
Other Secondary Þ					
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; 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 elexacaftor/tezacaftor/ivacaftor 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 favors Alyftrek.

The pre-specified non-inferiority margin was -3.0 percentage points.

Þ Not controlled for multiplicity.

Study 121-105

Study 121-105 was a multicohort, open-label study in people with CF with at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor. 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. 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 elexacaftor/tezacaftor/ivacaftor at baseline. The mean $ppFEV_1$ at baseline, on elexacaftor/tezacaftor/ivacaftor, was 99.7 percentage points (range: 29.3, 146.0) and the mean SwCl at baseline, on elexacaftor/tezacaftor/ivacaftor, 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 from Study 121-105, (Cohort B1)

Analysis	Statistic	Alyftrek 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.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of vanzacaftor, tezacaftor and deutivacaftor are similar between healthy adult subjects and people with CF. Following initiation of once-daily dosing vanzacaftor/tezacaftor/deutivacaftor plasma concentrations reach steady state within 20 days for vanzacaftor, within 8 days for tezacaftor, and within 8 days for deutivacaftor.

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

Table 7: Mean (SD) pharmacokinetic parameters of vanzacaftor, tezacaftor and deutivacaftor 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)**
vanzacaftor 20 mg/tezacaftor 100 mg /deutivacaftor 250 mg	vanzacaftor	0.812 (0.344)	18.6 (8.08)
	tezacaftor	6.77 (1.24)	89.5 (28.0)
	deutivacaftor	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

Vanzacaftor, tezacaftor, and deutivacaftor 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.

Vanzacaftor exposure (AUC) increases approximately 4- to 6-fold when administered with fat-containing meals relative to fasted conditions. deutivacaftor 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 tezacaftor (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Distribution

Vanzacaftor and deutivacaftor are > 99% bound to plasma protein, primarily to albumin and alpha 1-acid glycoprotein. Tezacaftor is approximately 99% bound to plasma proteins, primarily to albumin.

After oral administration of vanzacaftor/tezacaftor/deutivacaftor, the mean (SD) apparent volume of distribution of vanzacaftor, tezacaftor and deutivacaftor was 90.4 L (31.3), 123 L (43.2) and 157 L (47.3), respectively. Vanzacaftor, tezacaftor and deutivacaftor do not partition preferentially into human red blood cells.

Metabolism

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

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

Deutivacaftor is primarily metabolized by CYP3A4/5 to form the 2 major circulating metabolites, M1-deutivacaftor and M6-deutivacaftor. Relative to ivacaftor, deutivacaftor exhibited more metabolic stability and formed less M1-deutivacaftor, the deuterated-equivalent of M1-ivacaftor. M1-deutivacaftor has approximately one-fifth the potency of deutivacaftor and is considered pharmacologically active. M6-deutivacaftor is the other major metabolite of deutivacaftor, the deuterated-equivalent of M6-ivacaftor, and is not considered pharmacologically active.

Elimination

After oral administration of vanzacaftor/tezacaftor/deutivacaftor, the mean (SD) apparent clearance values of vanzacaftor, tezacaftor and deutivacaftor 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 vanzacaftor, tezacaftor and deutivacaftor following administration of the vanzacaftor/tezacaftor/deutivacaftor 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 vanzacaftor, tezacaftor and deutivacaftor following administration of the vanzacaftor/tezacaftor/deutivacaftor 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-vanzacaftor alone (91.6%), the majority of radioactivity was eliminated in faeces primarily as metabolites in the faeces.

Following oral administration of ^{14}C-tezacaftor alone, the majority of the dose (72%) was excreted in the faeces (unchanged or as the M2-tezacaftor) and about 14% was recovered in urine (mostly as M2-tezacaftor), resulting in a mean overall recovery of 86% up to 26 days after the dose.

Preclinical data indicate that the majority of ^{14}C-deutivacaftor and ^{14}C-ivacaftor are excreted in the faeces. Major excreted metabolites of deutivacaftor were M1-deutivacaftor and M6-deutivacaftor and major excreted metabolites for ivacaftor were M1-ivacaftor and M6-ivacaftor. The excretion of deutivacaftor in humans is expected to be similar to that of ivacaftor, based on similar structure (deuterated isotopologue) and nonclinical data.

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

Hepatic impairment

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

Renal impairment

Urinary excretion of vanzacaftor, tezacaftor, and deutivacaftor is negligible (see Elimination).

Vanzacaftor alone or in combination with tezacaftor and deutivacaftor 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, exposure of vanzacaftor was similar in patients with mild renal impairment (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 tezacaftor 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 deutivacaftor 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 DOSAGE AND METHOF OF ADMINISTRATION).

Gender

Based on population PK analysis, there are no clinically relevant differences in exposures of vanzacaftor, tezacaftor and deutivacaftor between males and females.

People with CF 6 to less than 18 years of age

Vanzacaftor, tezacaftor and deutivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 8. Exposure of vanzacaftor, tezacaftor and deutivacaftor in people 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 (N)	Dose	vanzacaftor $AUC_{0\text{-}24h}$ (mcg·h/mL)	tezacaftor $AUC_{0\text{-}24h}$ (mcg·h/mL)	deutivacaftor $AUC_{0\text{-}24h}$ (mcg·h/mL)
6 to < 12 years	< 40 kg (N = 70)	vanzacaftor 12 mg qd/ tezacaftor 60 mg qd/ deutivacaftor 150 mg qd	13.0 (4.90)	69.1 (20.7)	30.2 (11.6)
	≥ 40 kg (N = 8)	vanzacaftor 20 mg qd/ tezacaftor 100 mg qd/ deutivacaftor 250 mg qd	18.6 (7.49)	101 (33.7)	48.5 (18.7)
12 to < 18 years	(N = 66)	vanzacaftor 20 mg qd/ tezacaftor 100 mg qd/ deutivacaftor 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; $AUC_{0\text{-}24h}$: 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 at exposures greater than the maximum human exposure, indicating little relevance to clinical use.

Genotoxicity

Vanzacaftor

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

Vanzacaftor/tezacaftor/deutivacaftor

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

Fertility and Pregnancy

Vanzacaftor was not teratogenic in rats at 10 mg/kg/day nor at 40 mg/kg/day in rabbits (approximately 30 and 22 times, respectively, the maximum recommended human dose [MRHD] based on AUCs of vanzacaftor).

Vanzacaftor 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 vanzacaftor was observed in pregnant rats.

Carcinogenicity

Vanzacaftor

Vanzacaftor was shown to be non-carcinogenic in a 6 month study in Tg.rasH2 mice.

Tezacaftor

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

Deutivacaftor

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

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

Fertility and Pregnancy

The effect of deutivacaftor on fertility and pregnancy has not been evaluated; however, ivacaftor 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 ivacaftor). Slight decreases of the seminal vesicle weights were observed in males at 200 mg/kg/day dose (approximately 15 times the MRHD based on summed AUC of ivacaftor).

In a pre- and post-natal development study in pregnant rats at doses above 100 mg/kg/day (approximately 8 times the MRHD), ivacaftor 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 ivacaftor was observed in pregnant rats and rabbits.

Juvenile animals

Findings of cataracts were observed in juvenile rats dosed from post-natal Days 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.3 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in fetuses derived from rat dams treated with ivacaftor on gestation Days 7 to 17, in rat pups exposed to ivacaftor to a certain extent through milk ingestion up to post-natal Day 20, in 7-week-old rats, or in 3.5 to 5-month-old dogs treated with ivacaftor. The potential relevance of these findings in humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Alyftrek vanzacaftor/tezacaftor/deutivacaftor film-coated tablets:
Croscarmellose sodium
Hypromellose
Hypromellose acetate succinate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

Tablet film coat
Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg
OPADRY II Complete Film Coating System 20A100021 Purple

Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
OPADRY II Complete Film Coating System 20A100025 Purple

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Alyftrek 10/50/125 (vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg) film-coated tablets:

24 months

Alyftrek 4/20/50 (vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg) film-coated tablets:

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF THE CONTAINER

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

Pack sizes
Alyftrek 10/50/125 vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets: Pack size of 56 tablets

Alyftrek 4/20/50 vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets: Pack size of 84 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
P O Box 62027
Sylvia Park
AUCKLAND 1644
New Zealand
Telephone: (09) 918 5100
e-mail: VertexMedicalInfo@vrtx.com

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 16 OCT 2025

10 DATE OF REVISION

Summary of changes table

Section Changed	Summary of New Information
New Datasheet	