5 May 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Alyftrek
(deutivacaftor/tezacaftor/vanzacaftor)
Treatment of cystic fibrosis
EU/3/21/2527

Sponsor: Vertex Pharmaceuticals (Ireland) Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Product and administrative information

Product	
Designated active substance(s)	(14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor
Other name(s)	--
International Non-Proprietary Name	Deutivacaftor/tezacaftor/vanzacaftor
Tradename	Alyftrek
Orphan condition	Treatment of cystic fibrosis
Sponsor's details:	Vertex Pharmaceuticals (Ireland) Limited Unit 49 Block 5 Northwood Court Northwood Crescent Northwood Dublin 9 D09 T665 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vertex Pharmaceuticals (Ireland) Limited
COMP opinion	7 October 2021
EC decision	12 November 2021
EC registration number	EU/3/21/2527
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Peter Mol / Finbarr Leacy
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission	30 April 2024
Procedure start	23 May 2024
Procedure number	EMA/H/C/006382
Invented name	Alyftrek
Therapeutic indication	Treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Further information on Alyftrek can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/alyftrek
CHMP opinion	25 April 2025

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Enrico Costa / Elisabeth Johanne Rook
Sponsor's report submission	20 December 2024
COMP discussion and adoption of list of questions	14-15 April 2025
COMP opinion (adoption via written procedure)	5 May 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor was considered justified based on clinical data showing improvements in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and reductions in sweat chloride, following treatment with the product;
- the condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that, based on direct and indirect comparisons, the product has achieved a larger reduction in sweat chloride, an acceptable pharmacodynamic marker, as compared to the other CFTR modulators approved. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor as an orphan medicinal product for the orphan condition: treatment of cystic fibrosis.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. This gene is responsible for expression of a protein called the CF transmembrane conductance regulator. This protein regulates chloride transport. Over 2000 mutations in CFTR are found, but not all of them causes CF. The main pathogenetic mechanism in cystic fibrosis is a defect in the cellular Na+/Cl- transport pump, with defect in Na+ and Cl- regulation across the cellular membranes at the one known as CFTR site. The most common mutation is the deletion of phenylalanine at the 508 locus, referred to as delta (Δ) F508. CF patients have exocrine gland dysfunction involving multiple organ systems, with production of thick mucus in the bronchial tree, leading to bronchiectasis, chronic respiratory infections, and they present with pancreatic enzyme insufficiency and associated complications. The life-expectancy of CF has increased in the past years; however, most of the patients still die before the age of forty at the present date, mainly due to the pulmonary component of the disease.

The approved therapeutic indication "Alyftrek tablets are indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1)" falls within the scope of the designated orphan condition "Treatment of cystic fibrosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition since the time of orphan designation.

The condition remains life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

Number of people affected or at risk

There have been no significant changes in the prevalence of the condition since the time of orphan designation.

The sponsor estimates the prevalence of cystic fibrosis (CF) in Europe using data from the European Cystic Fibrosis Society Patient Registry (ECFSPR), which collects demographic and clinical information from consenting individuals with CF across European countries. As the exact prevalence of CF is not well-defined, the sponsor utilizes the 2021 ECFSPR report to derive an estimate.

To calculate prevalence, the sponsor first identifies country-specific CF case counts from the registry and applies adjustments based on the estimated coverage percentage of each country's registry data. This adjustment aims to approximate the total number of CF cases within each country. The sum of these estimated cases results in a total CF population estimate of 38,776 individuals across the EU and EEA (Table 1).

The prevalence estimate is derived by dividing the total estimated CF cases by the total population of the included countries, which is based on United Nations Population Division's 2022 World Population Prospects. This calculation results in an overall estimated prevalence of 0.86 cases per 10,000 persons, with country-specific prevalence ranging from 0.19 per 10,000 (Finland) to 2.99 per 10,000 (Ireland). These estimates remain below the 5 per 10,000 orphan designation threshold.

The sponsor's analysis provides an estimate of CF prevalence based on available registry data, adjusted case estimates, and population-based calculations. The findings indicate that CF remains within the prevalence threshold for orphan designation in the EU and EEA. Recently the COMP has often adopted approximately 1 in 10,000 so to allow for slight fluctuations of prevalence based on different sources. This figure is also used for the present application.

Table 1. Estimated Prevalence of CF in the EU/EEA

	ECFSR (2021 Report)[a]			**Estimated Prevalence**	
	CF Cases (n)	**Estimated Coverage (%)**	**Estimated CF Cases (n)**	**Total Population[b]**	**CF Cases Per 10,000 Persons**
Austria	877	>90	974	8,922,082	1.09
Belgium	1387	>90	1,541	11,611,420	1.33
Bulgaria	208	87	239	6,885,868	0.35
Croatia	148	>95	156	4,060,136	0.38
Cyprus	34	>80	43	1,244,188	0.34
Czech Republic	681	99	688	10,510,751	0.65
Denmark	561	99	567	5,854,241	0.97
Finland	97	90	108	5,535,992	0.19
France	7,136	>90	7,929	64,531,444	1.23
Germany	6,789	80	8,486	83,408,555	1.02
Greece	618	80	773	10,445,365	0.74
Hungary	508	98	518	9,709,786	0.53
Iceland	14	>90	16	370,335	0.42
Ireland	1,325	89	1,489	4,986,526	2.99
Italy	5,994	98	6,116	59,240,330	1.03
Latvia	47	>90	52	1,873,919	0.28
Lithuania	41	70	59	2,786,651	0.21
Luxembourg[c]	28	60	47	639,321	0.73
Netherlands	1,596	95	1,680	17,501,696	0.96
Norway	344	85	405	5,403,021	0.75
Poland	1,430	84	1,702	38,307,726	0.44
Portugal	366	>95	385	10,290,103	0.37

Romania	268	54	496	19,328,560	0.26
Slovakia	295	>90	328	5,447,622	0.60
Slovenia	118	>95	124	2,119,410	0.59
Spain	2,532	83	3,051	47,486,935	0.64
Sweden	765	>95	805	10,467,097	0.77
Total	**34,207**	**--**	**38,776**	**448,969,075**	**0.86**

EEA: European Economic Area; EU: European Union
[a] ECFSR (2021 Report) data not available for the following countries: Estonia, Malta, Liechtenstein, and Northern Ireland
[b] Total population based on United Nations, Population Division, World Population Prospects 2022
[c] In Luxembourg, an adult centre did not provide data for 2021.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor describes the current treatment landscape for cystic fibrosis (CF), noting that while there is no cure, available therapies fall into two main categories: (1) treatments that manage symptoms, complications, and comorbidities (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy), and (2) CF transmembrane conductance regulator (CFTR) modulators, which target the underlying cause of the disease. The introduction of CFTR modulators represents a significant advancement in CF treatment, as they have been shown to modify disease progression in patients with specific CFTR mutations, including severe (e.g., F508del, MF mutations, or gating mutations) and RF mutations.

The sponsor provides an overview of centrally authorized medicinal products for CF treatment in the European Union (EU) (Table 2).

In addition to centrally authorized treatments, several nationally authorized therapies are available, including generic antibiotics (e.g., ciprofloxacin, meropenem trihydrate), mucolytics (e.g., dornase alfa), and anti-inflammatory agents. Other supportive treatments, such as hypertonic saline (classified as a medical device) and chest physiotherapy, are also commonly used.

Table 2. Centrally Authorized Medicinal Products for the Treatment of CF

Invented Name (INN)	**Initial MAA Approval Date**	**Current Indication and Age Groups**
Products Targeting CFTR Dysfunction		
Kalydeco (ivacaftor)	23 Jul 2012	Kalydeco is indicated for the treatment of patients with CF aged 1 month and older and weighing 3 kg or more who have an *R117H CFTR* mutation (*R117H* patients) or 1 of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E, G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P, S549N* or *S549R* (Gating patients)

Orkambi (lumacaftor/ ivacaftor)	19 Nov 2015	Orkambi is indicated for the treatment of CF in patients aged 1 year and older who are homozygous for the *F508del* mutation (F/F patients).
Symkevi + Kalydeco (tezacaftor/ivacaftor)	31 Oct 2018	Symkevi is indicated in a combination regimen with Kalydeco for the treatment of patients with CF aged 6 years and older who are homozygous for the *F508del* mutation (F/F patients) or who are heterozygous for the *F508del* mutation and have 1 of the following mutations in the *CFTR* gene: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T* (F/RF patients).
Kaftrio (ELX/TEZ/IVA)	21 Aug 2020	Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of CF in patients aged 2 years and older who have at least one *F508del* mutation in the *CFTR* gene (F-any patients)
Products to Manage CF Symptoms		
Bronchitol (mannitol)	13 Apr 2012	Bronchitol is indicated for the treatment of CF in adults aged 18 years and above as an add-on therapy to best standard of care.
Cayston (aztreonam lysine)	21 Sep 2009	Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with CF aged 6 years and older.
Colobreathe (colistimethate sodium)	13 Feb 2012	Colobreathe is indicated for the management of chronic pulmonary infections due to *P aeruginosa* in patients with CF aged 6 years and older.
Quinsair (levofloxacin)	26 Mar 2015	Quinsair is indicated for the management of chronic pulmonary infections due to *P aeruginosa* in adult patients with CF.
TOBI Podhaler (tobramycin)	20 Jul 2011	TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to *P aeruginosa* in adults and children aged 6 years and older with CF.

Alyftrek (deutivacaftor/tezacaftor/vanzacaftor) has been recommended for the granting of a marketing authorization (MA) in the European Union (EU) for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1)

For further details on posology and clinical data, refer to the Summary of Product Characteristics (SmPC).

Comparison with existing cystic fibrosis therapies

Given its mechanism of action as a CFTR modulator, the relevant comparison is considered against other CFTR modulators that have already been authorized, rather than treatments that address only the symptoms or complications of cystic fibrosis (CF). While conventional CF therapies, such as mucolytics, antibiotics, bronchodilators, and pancreatic enzyme supplements, play a critical role in managing the symptoms and complications of cystic fibrosis, they do not correct for the underlying CFTR protein dysfunction that causes the disease. As a result, their therapeutic goals and mechanisms

of action are fundamentally different from those of CFTR modulators like Alyftrek, which directly target the defective protein. Although these therapies may continue to be used alongside CFTR modulators in clinical practice, they do not represent an appropriate comparator for evaluating the efficacy of a disease-modifying treatment. Therefore, comparisons should focus on other CFTR modulators that share a similar mechanism of action. This broader indication rests on in vitro responsiveness data, clinical data, and expert clinical input and was accepted by the CHMP as a valid basis for marketing-authorisation.

The Phase 3 clinical program for VNZ/TEZ/D-IVA (vanzacaftor/tezacaftor/deutivacaftor i.e. Alyftrek) was designed to establish its benefit–risk profile relative to the existing standard-of-care regimen ELX/TEZ/IVA (elexacaftor/tezacaftor/ivacaftor i.e. Kaftrio) in people with cystic fibrosis (CF) carrying at least one F508del or other triple-combination-responsive (TCR) mutation. Together, the three principal studies—Studies 102, 103 and 105 (Cohorts A1 and B1)—enrolled genotypes representing 94 % of the CF population eligible for Kaftrio.

Studies 102 and 103 were randomized, double-blind, parallel-group, active-controlled trials in subjects aged ≥ 12 years. Each began with a four-week run-in period on ELX/TEZ/IVA to establish a consistent baseline, followed by 52 weeks of either continued ELX/TEZ/IVA or switch to VNZ/TEZ/D-IVA. Study 102 enrolled F/MF subjects (heterozygous for F508del and a minimal-function mutation) and Study 103 enrolled F/F, F/RF, F/G and TCR/non-F subjects. The primary endpoint was absolute change from baseline in ppFEV1 through Week 24, which was tested for non-inferiority. The first key secondary efficacy endpoint was the absolute change from baseline in SwCl through Week 24.

The pivotal clinical studies 102 (F/MF) and 103 (F/F, F/RF, F/G and TCR/non-F) showed no difference in lung function (ppFEV1) between Alyftrek and Kaftrio through 24 weeks of treatment. Study 102 demonstrated the efficacy for the F mutation as the MF mutation will not respond, the F/F, F/RG and F/G data provide supportive evidence for the efficacy in pwCF who harbour at least one F mutation. This was a study aimed at showing non-inferiority of Alyftrek vs Kaftrio.

Differences in the size of the effect on SwCl were observed in studies 102 and 103, with a more pronounced effect of VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA on the F/MF subjects in study 102 than on the heterogeneous study population of study 103. However, the clinical relevance of this difference has not been established. To contextualize these observations, the sponsor relies on natural history data and pooled analysis of clinical study data indicating that lower sweat-chloride levels could correlate with better clinical outcomes in cystic fibrosis.

These key secondary outcomes on this pharmacodynamic endpoint support the results of the primary endpoint. Across all phase 3 studies, subgroup analyses by age, sex, geographic region, baseline $ppFEV_1$, SwCl and genotype yielded consistent treatment effects.

This new fixed combination shows similarities with ELX/TEZ/IVA (Kaftrio). Compared to Kaftrio (ELX/TEZ/IVA), the ELX active substance in Kaftrio has been replaced in Alyftrek by the active substance VNZ. D-IVA is a deuterated isotopologue of ivacaftor with a similar chemical structure with a comparable PD profile. D-IVA is administered in a higher dose than IVA, and this product can be administered once daily compared with currently approved modulator treatments administered twice daily. The sponsor points to a once-daily dosing regimen-taken with a single fat-containing meal -as potentially reducing pill burden and supporting adherence, compared with more frequent dosing schedules with Kaftrio.

In addition, the Committee for Orphan Medicinal Products (COMP) recognised that Alyftrek addresses patient groups for whom no other CFTR modulators were already authorised at the time of the COMP assessment, and that the conventional symptom-focused therapies—while important—do not correct

the underlying defect. These considerations underpin the COMP's conclusion that Alyftrek continues to fulfil the criteria for orphan designation, by offering a novel, targeted option where previous treatments have been insufficient.

Significant benefit

Not applicable.

4. COMP position adopted on 5 May 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of cystic fibrosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Alyftrek.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Alyftrek, (14S)-8-[3-(2-{dispiro[2.0.24.13]heptan-7-yl}ethoxy)-1H-pyrazol-1-yl]-12,12-dimethyl-2lamba6-thia-3,9,11,18,23-penta-azatetracyclo[17.3.1.111,14.05,10]tetracosa-1(22),5,7,9,19(23),20-hexaene-2,2,4-trione calcium salt hydrate, deutivacaftor, tezacaftor (deutivacaftor/tezacaftor/vanzacaftor) for treatment of cystic fibrosis (EU/3/21/2527) is not removed from the Community Register of Orphan Medicinal Products.