Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

VX-659/tezacaftor/ivacaftor (fixed-dose combination) for cystic fibrosis homozygous for F508del mutation in patients aged 12 years and older

NIHRIO ID	18332	**NICE ID**	9986
Developer/Company	Vertex Pharmaceuticals Inc	**UKPS ID**	Not Available

Licensing and market availability plans	Phase III clinical trial completed.

SUMMARY

The triple fixed-dose combination (FDC), VX-659/tezacaftor/ivacaftor-FDC, is in clinical development for cystic fibrosis (CF) that is homozygous for F508del mutation for patients aged 12 years and older. CF is a life-limiting inherited disease that affects about 10,000 people in the UK. Genetic mutations affect the CF transmembrane conductance regulator (CFTR) gene, which is essential for the regulation of salt and water movements across cell membranes. These mutations mean that the CFTR protein is not processed and moved through the cells normally, resulting in little to no CFTR protein at the cell surface. This results in thickened secretions in organs with epithelial cell lining, mainly affecting the lungs and digestive system.

VX-659 and tezacaftor are designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the F508del CFTR protein. Ivacaftor is designed to enhance the function of the CFTR protein once it reaches the cell surface. The triple therapy of VX-659/tezacaftor/ivacaftor-FDC may result in an effective therapeutic option for people with CF with F508del mutations, who currently have limited options.

PROPOSED INDICATION

Cystic fibrosis (CF) homozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/F), patients aged 12 years and older.[1]

TECHNOLOGY

DESCRIPTION

The triple fixed-dose combination (FDC) of VX-659, tezacaftor and ivacaftor (VX659/tezacaftor/ivacaftor-FDC) is in clinical development for patients aged 12 years and older who have CF that is homozygous for F508del mutation in the CFTR gene (F/F).[1]

VX-659 is a next-generation CFTR corrector whose mechanism of action is based on clear additivity on functional and biochemical assays of CFTR processing, trafficking and function in vitro.[2]

Tezacaftor is a selective CFTR corrector that binds to the first Membrane Spanning Domain (MSD-1) of CFTR. Tezacaftor facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface, resulting in increased chloride transport in vitro.[3]

Ivacaftor is a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either active substance alone. The combination targets the abnormal CFTR protein by increasing the quantity and function of CFTR at the cell surface and subsequently increasing airway surface liquid height, and ciliary beat frequency in vitro in human bronchial epithelial (HBE) cells from homozygous F508del CF patients. The exact mechanisms by which tezacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.[3]

In the phase III clinical trial NCT03460990, patients were administered the triple FDC tablets of VX-659 240mg, tezacaftor 100mg and ivacaftor 150mg in the morning, followed by ivacaftor 150mg single tablet in the evening.[4] There is also a phase III extension study NCT03447262, in which patients receive active treatment for up to 96 weeks.[5]

INNOVATION AND/OR ADVANTAGES

Whilst the dual combination of a first-generation CFTR corrector (lumacaftor or tezacaftor) and ivacaftor provides both short-term and long-term benefit to patients with F/F genotype, these combinations do not fully restore function to F508del CFTR protein.[2]

It has been shown in vitro that a combination of two correctors with distinct binding sites on CFTR and complementary mechanisms of action can increase the amount of F508del CFTR protein at the cell surface to a greater extent than either corrector alone. VX-659 has therefore been developed for use in combination with tezacaftor and ivacaftor to increase both the amount and function of F508del CFTR protein to a greater extent than a dual combination of a corrector and a potentiator. Additivity of VX-659 to tezacaftor and ivacaftor in vitro increases F508del CFTR protein processing within the cell and trafficking to the cell surface. Because tezacaftor and VX-659 work through different mechanisms, it is believed that the combination will increase the amount of F508del CFTR protein at the cell surface more than either compound alone, an effect that could be potentiated by ivacaftor to further increase chloride transport.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

VX-659/tezacaftor/ivacaftor-FDC does not currently have Marketing Authorisation in the EU/UK for any indication.

The treatment regimen of VX-659/tezacaftor/ivacaftor-FDC was granted orphan drug designation in the EU in December 2018 for the treatment of CF.[6]

The medicinal product Symkevi® (100mg tezacaftor and 150mg ivacaftor) in a combination regimen with Kalydeco® (150mg ivacaftor) has been granted Marketing Authorisation in the EU for patients aged 12 years and older with CF with F/F genotype or with CF heterozygous for F508del mutation and have one of another number of listed mutations.[7] Very common adverse effects (>10%) in patients treated with Symkevi in combination with ivacaftor include nasopharyngitis and headache.[3]

The medicinal product Symkevi® (100mg tezacaftor and 150mg ivacaftor) was designated an orphan drug in the EU in February 2017, and this designation was maintained at the time of Marketing Authorisation.[8]

The medicinal product Kalydeco® (150mg ivacaftor) has been granted Marketing Authorisation in the EU for:[9]

- the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R
- the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the CFTR gene

The medicinal product Kalydeco® (150mg ivacaftor) was designated an orphan drug in the EU in July 2008, and this designation was maintained at the time of Marketing Authorisation.[10]

VX-659/tezacaftor/ivacaftor-FDC is in phase III clinical development for patients aged 6 to 11 years with CF with F/F or F/MF genotypes.[11]

PATIENT GROUP

DISEASE BACKGROUND

CF results from mutations affecting a gene that encodes for the CFTR (a chloride channel) which is essential for the regulation of salt and water movements across cell membranes. Absent or reduced function of CFTR results in thickened secretions in organs with epithelial cell lining, hence it is multi-system, although mainly affects the lungs, digestive system and vas deferens (part of the male reproductive system).[12]

In CF, the airways become clogged with thick sticky mucus, which impairs the clearance of microorganisms. This leads to recurrent infection, inflammation, bronchial damage, bronchiectasis and eventually death from respiratory failure. Patients are often infected with *S. aureus* and *P. aeruginosa*, but also by a number of other organisms, some of which are resistant to many antibiotics.[12]

In about 85% of cases the pancreatic exocrine ducts become sufficiently blocked to cause maldigestion and intestinal malabsorption (pancreatic insufficiency). Infants may fail to thrive, and older children and adults may become under-nourished. Appetite is often adversely affected which is a problem as there is an underlying increase in metabolic demands leading to a need for an

increased energy intake. Other complications include male infertility, CF-related diabetes, chronic liver disease and portal hypertension, joints affected by CF-arthropathy, bones affected by reduced bone mineral density, and behavioural and psychological problems associated with a sever long-term medical condition.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Cystic fibrosis (CF) is the most common, life-limiting recessively inherited disease in the UK.[12]
The latest annual report from the UK Cystic Fibrosis Registry shows that in 2017:[13]

- 10,469 people in the UK had a diagnosis of CF
- 214 patients were newly-diagnosed, of which 172 were identified by newborn screening
- 132 people with CF died, and the median age at death was 31 years
- 6,878 patients were aged 12 years and older (69.6% of patients who had annual reviews)
- 9,818 (99.3%) patients have been genotyped, of which 4,956 (49.1%) were homozygous for F508del mutation

In England in 2017/18 there were 13,592 hospital admissions with a primary diagnosis of CF (ICD-10 code E84), resulting in 88,098 finished consultant episode (FCE) bed days.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Care for people with CF should be provided by a specialist CF multidisciplinary team (MDT) based at a specialist CF centre. The MDT should include specialist paediatricians or adult physicians, nurses, physiotherapists, dietitians, pharmacists and clinical psychologists. Patients should have a comprehensive annual review, and routine reviews at regular intervals.[15]

Current treatments for CF manage the symptoms and complications rather than the cause of the disease.[16]

CURRENT TREATMENT OPTIONS

Treatments can be broadly classified as:

- nutritional repletion (for example, pancreatic enzymes and nutritional supplements)
- relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators)
- treatment of acute infections
- suppression of chronic infection
- suppression of inflammation (for example, steroids, high dose ibuprofen)
- lung transplantation[16]

NICE recommends mannitol dry powder for inhalation as an option for treating CF in adults who cannot use rhDNase and whose lung function is rapidly declining and for whom other osmotic agents are not considered appropriate.[17]

The medicinal product Orkambi® (lumacaftor and ivacaftor combination regimen) has a Marketing Authorisation in the UK for the treatment of patients aged 12 years and older with CF with F/F genotype, but is not recommended by NICE.[18,19]

PLACE OF TECHNOLOGY

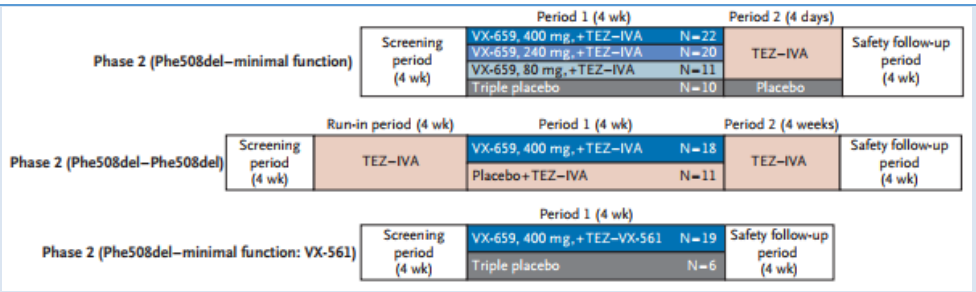
If licensed, VX-659/tezacaftor/ivacaftor-FDC will offer an additional treatment option for patients aged 12 years and older with CF with F/F genotype, who currently have few effective therapies available.[2]

CLINICAL TRIAL INFORMATION

Trial	**NCT03460990, EudraCT-2017-004133-82, VX17-659-103; homozygous for F508del mutation (F/F); VX-659–tezacaftor–ivacaftor vs tezacaftor–ivacaftor; phase III**	**NCT03447262, EudraCT-2017-004134-29, VX17-659-105; heterozygous for F508del mutation and a minimal function (MF) mutation (F/MF) or homozygous for F508del mutation (F/F); VX-659–tezacaftor–ivacaftor; phase III extension**
Sponsor	Vertex Pharmaceuticals Inc	Vertex Pharmaceuticals Inc
Status	Complete but unpublished	Ongoing
Source of Information	Trial registry,[4] press release[1]	Trial registry[5]
Location	EU (incl UK), USA and Australia	EU (incl UK), USA, Canada, Israel and Australia
Design	Randomised, active-controlled	Single group assignment, open label
Participants	n=111; aged 12 yrs and older; cystic fibrosis; homozygous for F508del mutation (F/F); forced expiratory volume in 1 second (FEV1) value ≥40% and ≤90% of predicted mean for age, sex and height	Previously participated in parent studies NCT03447249 or NCT03460990
Schedule	Run-in: tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening Pts then randomised to: • Experimental arm: Fixed dose combination (FDC) of VX-659 240mg / tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening. • Active comparator: FDC of placebo 240mg / tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening	Fixed dose combination (FDC) of VX-659 240mg / tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening
Follow-up	4-wk run-in prior to randomisation, active treatment for 4 wks, safety follow-up for 4 wks	Active treatment up to 96 wks, safety follow-up for up to 100 wks
Primary Outcomes	Absolute change in percent predicted FEV1 (ppFEV1) [Time frame: from	Safety and tolerability of long-term treatment based on adverse events (AEs) [Time frame: from baseline

	baseline at wk 4]. Baseline is end of run-in period.	through safety follow-up (up to 100 wks)]
Secondary Outcomes	• Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score [Time frame: from baseline at wk 4] • Absolute change in sweat chloride [Time frame: from baseline at wk 4] • Safety and tolerability assessed by number of subjects with AEs and serious adverse events (SAEs) [Time frame: from baseline through 4-wk safety follow-up (up to 12 wks)] • Observed pre-dose concentration (Ctrough) of VX-659, tezacaftor, metabolite M1-tezacaftor, and ivacaftor [Time frame: from day 1 through wk 4]	Time frame: from baseline through last dose of study drug (up to 96 wks): • Absolute change from baseline in ppFEV1 • Absolute change in sweat chloride • Number of pulmonary exacerbations (PEx) • Time to first PEx • Absolute change in body mass index (BMI) • Absolute change in BMI z-score • Absolute change in body weight • Absolute change from baseline in CFQ-R respiratory domain score
Key Results	Mean absolute improvement in ppFEV1 of 10.0 % points from baseline at wk 4 in VX-659–tezacaftor–ivacaftor group compared to placebo–tezacaftor–ivacaftor group ($p<0.0001$). Mean absolute within-group improvement in ppFEV1 from baseline for VX-659–tezacaftor–ivacaftor group was 10.2 % points at wk 4. Mean absolute within-group change in ppFEV1 from baseline for placebo–tezacaftor–ivacaftor group was 0.3 % points at wk 4.	-
Adverse effects (AEs)	VX-659–tezacaftor–ivacaftor FDC regimen generally well tolerated.	-
Expected reporting date	Study completion date reported as October 2018. Additional safety and efficacy data, including key secondary endpoints, to be disclosed H2 2019.	Study completion date reported as April 2021.

Trial	**NCT03224351, EudraCT-2016-003585-11, VX16-659-101; VX-659–tezacaftor–ivacaftor or VX-659–tezacaftor–VX-561 vs placebo; phase II**
Sponsor	Vertex Pharmaceuticals Inc
Status	Published
Source of Information	Publication,[2] trial registry[20]
Location	EU (incl UK), USA and Israel
Design	Randomised, placebo-controlled
Participants	n=124; aged 18 yrs and older; cystic fibrosis; heterozygous for F508del mutation and a MF mutation (F/MF), or homozygous for F508del mutation (F/F); FEV1 value ≥40% and ≤90% of predicted mean for age, sex and height

Schedule	
Follow-up	See chart above
Primary Outcomes	• Safety and tolerability assessed by number of subjects with AEs and SAEs [Time frame: from baseline through safety follow-up (20 wk)] • Absolute change in ppFEV1 [Time frame: from baseline through day 29]
Secondary Outcomes	Time frame: from baseline through day 29: • Absolute change in sweat chloride concentrations • Relative change in ppFEV1 • Absolute change in CFQ-R respiratory domain score Time frame: from day 1 through day 29: • Maximum observed concentration (Cmax) of VX-659, tezacaftor, metabolite M1-tezacaftor, ivacaftor, metabolite M1-ivacaftor and VX-561 • Area under the concentration versus time curve during a dosing interval (AUCtau) of VX-659, tezacaftor, metabolite M1-tezacaftor, ivacaftor, metabolite M1-ivacaftor and VX-561 • Observed pre-dose concentration (Ctrough) of VX-659, tezacaftor, metabolite M1-tezacaftor, ivacaftor, metabolite M1-ivacaftor and VX-561
Key Results	VX-659–tezacaftor–ivacaftor had an acceptable safety and side-effect profile. VX-659–tezacaftor–ivacaftor resulted in significant mean increases in the % of predicted FEV1 through day 29 ($P<0.001$) of up to 13.3 points in pts with F/MF; in pts with F/F already receiving tezacaftor–ivacaftor, adding VX-659 resulted in a further 9.7-point increase in the % of predicted FEV1. The sweat chloride concentrations and scores on the respiratory domain of the CFQ-R improved in both pt populations.
Adverse effects (AEs)	Most pts who received VX-659–tezacaftor–ivacaftor (57 of 71 pts [80%]), triple placebo (9 of 10 [90%]), or tezacaftor–ivacaftor (9 of 11 [82%]) reported having at least one AE. Among those receiving VX-659–tezacaftor-ivacaftor who had an AE, the maximum severity was mild or moderate for the majority of pts (53 of 57 pts [93%]). The most commonly observed AEs (>10% occurrence in the pooled VX-659–tezacaftor–ivacaftor groups) were cough, infective pulmonary exacerbation of cystic fibrosis, headache, oropharyngeal pain, and increased sputum production. Four AEs in pts receiving VX-659–tezacaftor–ivacaftor therapy were considered to be severe by site investigators. SAEs were reported in 7 pts (10%) who received VX-659–tezacaftor–ivacaftor, 3 pts (30%) who received triple placebo, and 2 pts (18%) who received tezacaftor–ivacaftor control. Most SAEs were infective pulmonary exacerbations of CF requiring hospitalization. No deaths occurred during the trial. There were no AEs leading to discontinuation of the trial regimen in any pts who received VX-659–tezacaftor–ivacaftor.

ESTIMATED COST

The cost of the treatment regimen of VX-659/tezacaftor/ivacaftor-FDC is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years homozygous for the F508del mutation (ID1486). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation (ID1303). Expected date of issue to be confirmed.
- NICE technology appraisal. Lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (TA398). July 2016.
- NICE technology appraisal. Mannitol dry powder for inhalation for treating cystic fibrosis (TA266). November 2012.
- NICE guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard. Cystic fibrosis (QS168). May 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Service Specification: Cystic fibrosis (adults). A01/S/a.
- NHS England. Service Specification: Cystic fibrosis (children). A01/S/b.

OTHER GUIDANCE

- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK. Second ed. December 2011.[12]

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