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Health Technology Briefing
August 2023

Vanzacaftor-tezacaftor-deutivacaftor for the treatment of cystic fibrosis

Company/Developer	Vertex Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27712	NICE TSID: Not available	UKPS ID: 669217

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Vanzacaftor-tezacaftor-deutivacaftor is in development for the treatment of cystic fibrosis in patients with at least one F508del mutation (faulty gene). Cystic fibrosis is a rare, chronic, and life-shortening genetic disease caused by a faulty gene that affects the movement of salt and water in and out of cells. It is a progressive, multi-system disease that affects the lungs, liver, gastrointestinal tract, pancreas, sinuses, sweat glands and reproductive tract. In the lungs, this leads to the build-up of abnormally thick, sticky mucus that can cause chronic lung infections and inflammation, resulting in progressive lung damage and premature death in many people with cystic fibrosis. It is an inherited condition, and the symptoms include recurring chest infections, wheezing, coughing, shortness of breath, damage to the airways and jaundice. Current treatment options have limited efficacy in some patients with cystic fibrosis.

Vanzacaftor-tezacaftor-deutivacaftor is a triple combination tablet being developed as a once-daily oral treatment for cystic fibrosis. When administered, vanzacaftor-tezacaftor-deutivacaftor is expected to further increase chloride transportation through the cell. If licensed, vanzacaftor-tezacaftor-deutivacaftor may provide a new combination treatment option for patients with cystic fibrosis, who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Proposed Indication

Treatment of cystic fibrosis in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1,2]

Technology

Description

Vanzacaftor-tezacaftor-deutivacaftor (VX-121-VX661-VX561) is a triple combination tablet being developed as an investigational once-daily treatment.[3,4] Vanzacaftor (VX121) is a novel cystic fibrosis transmembrane conductance regulator (CFTR) corrector, and both vanzacaftor and tezacaftor (VX-661) are designed to increase the amount of mature protein at the surface of a cell by targeting the processing and trafficking defect of the CFTR protein.[3,4] Deutivacaftor (VX561) is a novel CFTR potentiator that has been shown to have a reduced rate of clearance, increased exposure, greater plasma concentrations at 24 hours, and a longer half-life compared with other CFTR potentiators, thereby supporting once-daily dosing.[4,5]

In a phase III clinical trial (NCT05844449), participants aged 6 years and above will receive a once-daily oral tablet of vanzacaftor-tezacaftor-deutivacaftor at doses determined based on their age and weight.[1]

Key Innovation

There is an existing transformative treatment option for patients with cystic fibrosis who have at least one F508del allele. However, only a small number of people with cystic fibrosis receiving this treatment achieve sweat chloride concentrations similar to those seen in people with a single copy of a cystic fibrosis-causing mutation (cystic fibrosis carriers) who typically have no symptoms.[4]

Vanzacaftor-tezacaftor-deutivacaftor is expected to further increase the CFTR-mediated chloride transport through once-daily dosing. In a phase II trial, the new triple combination regimen of vanzacaftor-tezacaftor-deutivacaftor was shown to be safe and well tolerated and resulted in improved lung function, respiratory symptoms, and CFTR function.[4]

If licensed, vanzacaftor-tezacaftor-deutivacaftor may provide a new treatment option for patients with cystic fibrosis, who have at least one F508del mutation in the cystic fibrosis CFTR gene.

Regulatory & Development Status

Vanzacaftor-tezacaftor-deutivacaftor does not currently have Marketing Authorisation in the EU/UK for any indication.

Deutivacaftor as a monotherapy or in combination does not currently have Marketing Authorisation in the EU/UK for any indication.

Vanzacaftor as a monotherapy or in combination does not currently have Marketing Authorisation in the EU/UK for any indication.

Tezacaftor has Marketing Authorisation in the EU/UK as a combination therapy for the treatment of cystic fibrosis.[6]

Vanzacaftor-tezacaftor-deutivacaftor has been awarded an orphan designation in 2020, and a Fast Track designation by the U.S. Food and Drug Administration for the treatment of cystic fibrosis.[7,8]

Vanzacaftor-tezacaftor-deutivacaftor is also in phase II/III development for the treatment of cystic fibrosis in various age groups.[9]

Patient Group

Disease Area and Clinical Need

Cystic fibrosis is a life-limiting autosomal recessive disease caused by mutations in the sCFTR gene, which encodes an ion channel involved in the transport of chloride and bicarbonate.[4]. Autosomal recessive is a pattern of inheritance characteristic of some genetic disorders. Autosomal means that the gene in question is located on one of the numbered, or non-sex, chromosomes. Recessive means that two copies of the mutated gene (one from each parent) are required to cause the disorder.[5] The symptoms of cystic fibrosis include; recurring chest infections, wheezing, coughing, shortness of breath, damage to the airways and jaundice.[10] Cystic fibrosis is a genetic condition caused by a faulty gene that affect the movement of salt and water in and out of cells.[10] Approximately, 90% of cystic fibrosis patients have at least one F508del-CFTL allele (at least one F508del mutation in their CFTR gene).[4]

About 10,800 people in the UK are estimated to have cystic fibrosis, which represent 1 in every 2,500 babies born.[11] Also, it is estimated that around 1 in every 25 people in the UK are carriers of cystic fibrosis.[10] In England (2021-22) there were 8,127 finished consultant episodes (FCEs) and 6,939 admissions for cystic fibrosis (ICD-10 code E84), which resulted in 3,524 day cases and 35,502 FCE bed days.[12]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends mannitol dry powder for inhalation for the treatment of cystic fibrosis where the patients have at least one F508del mutation in the CFTR gene.[13] Other treatment options include ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor currently in development for treating cystic fibrosis.[14]

Clinical Trial Information

Trial	NCT05422222; EudraCT 2021-005930-40; A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-121/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 Years of Age **Phase III** – Recruiting **Location(s):** Four EU countries, UK, US, Australia and others **Primary completion date:** June 2030	NCT05844449; A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of Vanzacaftor/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Year of Age and Older **Phase III** – Not yet recruiting **Location(s):** unknown **Primary completion date:** Oct 2030
Trial Design	Non-randomised, open label, and sequential assignment	Single group assignment and open label interventional design
Population	N=210 (estimated); children aged 1 to 11 years with stable CF and at least 1 TCR mutation (including F508del) in the CFTR gene	N=180 (estimated); children and adults aged 6 years and above who have completed study drug treatment in the parent study (VX21-121-105; NCT Number: NCT05422222)

Intervention(s)	Part A: Oral administration of a fixed-dose combination tablet of Vanzacaftor-Tezacaftor-Deutivacaftor in the morning Part B: Oral administration of a fixed-dose combination tablet of Vanzacaftor-Tezacaftor-Deutivacaftor in the morning with dose(s) to be based on the outcome of Part A	Oral administration of a fixed-dose combination tablet of Vanzacaftor-Tezacaftor-Deutivacaftor
Comparator(s)	-	-
Outcome(s)	Primary outcome measures - Part A: Observed Pre-dose Plasma Concentration (Ctrough) of Vanzacaftor-Tezacaftor-Deutivacaftor, and Relevant Metabolites [Time frame: From Day 1 up to Day 22] - Part A: Safety and Tolerability as Assessed by Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time frame: From Day 1 up to Day 50] - Part B: Safety and Tolerability as Assessed by Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time frame: From Day 1 up to Week 28] See trial record for a full list of other outcomes.	Primary outcome measures: - Safety and Tolerability as Assessed by Number of Participants with Adverse Events (AEs) [Time frame: From Day 1 up to Week 100] See trial record for a full list of other outcomes.
Results (efficacy)	-	-
Results (safety)	-	-

Trial	NCT05076149; EudraCT 2021-000694-85; A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in

	Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) **Phase III** – Active, not recruiting **Location(s):** Thirteen EU countries, UK, US, Australia, Canada and others **Primary completion date:** May 2023
Trial Design	Randomised, parallel assignment, quadruple masked, double blinded and active comparator controlled
Population	N=600 (actual); children and adults aged 12 years and above with homozygous for F508del, heterozygous for F508del and a gating (F/G) mutation, heterozygous for F508del and a residual function (F/RF) mutation and at least 1 other TCR CFTR gene mutation identified as responsive to Elexacaftor-Tezacaftor-Ivacaftor and no F508del mutation
Intervention(s)	Oral administration of a fixed-dose combination tablet of Vanzacaftor-Tezacaftor-Deutivacaftor
Comparator(s)	Oral administration of a fixed-dose combination tablet of Elexacaftor-Tezacaftor-Ivacaftor
Outcome(s)	Primary outcome measures: - Absolute Change from Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 24 [Time frame: From Baseline Through Week 24] See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT05444257; A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-121 Combination Therapy in Subjects with Cystic Fibrosis **Phase III** – Enrolling by invitation **Location(s):** Thirteen EU countries, UK, US, Australia, Canada and others **Primary completion date:** Oct 2025
Trial Design	Single group assignment and open label interventional design
Population	N=850 (estimated); children and adults aged 12 years and above who completed study drug treatment in a parent study VX20-121-102 (NCT05033080) and VX20-121-103 (NCT05076149); or had study drug interruption(s) in a parent study but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period in the parent study
Intervention(s)	Oral administration of a fixed-dose combination tablet of Vanzacaftor-Tezacaftor-Deutivacaftor
Comparator(s)	-

Outcome(s)	Primary outcome measures: - Safety and Tolerability as Assessed by Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time frame: From Day 1 up to Week 100] See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT05033080; EudraCT 2021-000712-31; A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects with Cystic Fibrosis (CF) Who Are Heterozygous for F508del and a Minimal Function Mutation (F/MF) **Phase III** – Active, not recruiting **Location(s):** Seven EU countries, UK, US, Australia and others **Primary completion date:** May 2023
Trial Design	Randomised, parallel assignment, quadruple masked, double blinded and active comparator controlled
Population	N=436 (actual); children and adults aged 12 years and above with Heterozygous for F508del and a minimal function mutation (F/MF genotype)
Intervention(s)	Oral administration of a fixed-dose combination tablet of Vanzacaftor-Tezacaftor-Deutivacaftor
Comparator(s)	Oral administration of a fixed-dose combination tablet of Elexacaftor-Tezacaftor-Ivacaftor
Outcome(s)	Primary outcome measures: - Absolute Change from Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 24 [Time frame: From Baseline Through Week 24] See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03912233; A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older with Cystic Fibrosis.

	Phase II – Completed **Location(s):** Three EU countries, UK and US **Primary completion date:** December 2019
Trial Design	Randomised, sequential assignment, quadruple masked, active comparator controlled
Population	N=87 (actual); adults aged 18 years and above with heterozygous for F508del and MF mutation (F/MF), and homozygous for F508del (F/F)
Intervention(s)	Oral dose of Vanzacaftor (5 mg) once daily, Tezacaftor (100 mg), Deutivacaftor (150 mg) for four weeks
Comparator(s)	Part 1: Placebo comparator matched to Vanzacaftor-Tezacaftor-Deutivacaftor triple combination for four weeks. Part 2: Active comparator TEZ/IVA: Tezacaftor (100 mg), Ivacaftor (150 mg)
Outcome(s)	Primary outcome measures: - Safety and Tolerability as Assessed by Number of Participants with Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time frame: From Day 1 Through Safety Follow-up (up to Day 75 for Part 1 and up to Day 85 for Part 2)] - Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) [Time frame: From Baseline Through Day 29] See trial record for a full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of vanzacaftor-tezacaftor-deutivacaftor is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis. (GID-TA11187). Expected publication date: February 2024.
- NICE technology appraisal guidance. 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
- NICE medtech innovation briefing. (MIB219). CFHealthHub for managing cystic fibrosis during the COVID-19 pandemic. (MIB219). July 2020

NHS England (Policy/Commissioning) Guidance

- NHS England. 2023 Commissioning Statement: Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for cystic fibrosis. 210508Pa.
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- NHS England. 2014 NHS Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. A01/P/b.
- NHS England. 2014 NHS Clinical Commissioning Urgent Policy Statement: Ivacaftor and tezacaftor/ivacaftor for cystic fibrosis: "off-label" use in patients with named rarer mutations. 200809P.

Other Guidance

- Southern KW, Castellani C, Lammertyn E, Smyth A, *et al.* Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. 2023[15]
- Cystic Fibrosis Trust. Pharmacy standards in cystic fibrosis care in the UK. 2022.[16]
- Castellani C, Duff AJA, Bell SC, Heijerman HGM, *et al*. ECFS best practice guidelines: the 2018 revision. 2018[17]
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- Stern M, Bertrand DP, Bignamini E, Corey M, Dembski B, Goss CH, Pressler T, Rault G, Viviani L, Elborn JS, Castellani C. European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis. 2014.[19]
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Additional Information

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Trial ID: NCT05844449. 2023. Status: Not yet recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05844449#contacts [Accessed 24 July 2023].

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.