Health Technology Briefing
May 2022

Kaftrio (Elexacaftor/tezacaftor/ivacaftor) and ivacaftor for treating cystic fibrosis in children (2 to 5 years) with at least one F508del mutation in the CFTR gene

Company/Developer	Vertex Pharmaceuticals Inc.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30517	NICE ID: 10767	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Kaftrio (Elexacaftor(ELX)/tezacaftor(TEZ)/ivacaftor(IVA)) is a triple combination drug that is licensed for patients with cystic fibrosis (CF) aged 6 years and older and is being investigated for use in patients aged 2 to 5 years. CF is an inherited disease that progressively effects the lungs and digestive system causing breathing difficulties and problems absorbing nutrients from food. There are currently no licensed medicines or combinations that act on all variations of F508del mutations that cause the symptoms and damage in CF for patients under 6 years old. Existing treatments are limited to certain populations leaving others without treatment options. Kaftrio would provide an option to those previously excluded from these treatments.

Kaftrio changes proteins on the surface of cells to make them function more normally and improve the quantity, making the mucus in the lungs and digestive system less thick, reducing symptoms in the patient and limiting the inflammation and damage caused by the mucus. Kaftrio is administered orally once a day in the morning followed by an oral administration of IVA alone in the evening to maintain its effectiveness. Kaftrio and IVA have demonstrated improved quality of life respiratory scores and lung function in older population patients (6 years and older) with slow damage to the lungs and digestive system, lowing mortality, pulmonary exacerbations, and lung transplants.

Proposed Indication

For the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years old that have at least one F508del mutation in the CFTR gene.[1]

Technology

Description

Kaftrio (Trikafta, Elexacaftor(ELX)/tezacaftor(TEZ)/ivacaftor(IVA)) is a fixed dose combination drug in development for the treatment of CF in children aged 2 to 5 years old with at least one F508del mutation in the CFTR gene.[1,2] Kaftrio acts as a CF transmembrane conductance regulator (CFTR) modulating therapy that contains two correctors (TEZ and ELX) that work by facilitating correct folding and presentation of the mature CFTR protein on a cells surface, and a potentiator of the CFTR channel (IVA) allowing for an increase in chloride ion flow.[3] These actions are expected to make mucus and digestive juices less thick, thereby helping to relieve symptoms of the disease.[4] Although ELX and TEZ are administered once a day with IVA in the oral fixed dose combination, IVA requires twice daily dosing with a 12 hour gap as its metabolite only maintains 1/6th of the non-metabolised potency unlike ELX and TEZ.[3]

In the phase III clinical trial (NCT04537793), the fixed-dose combination kaftrio was administered orally in the morning, followed by oral IVA in the evening.[1]

Key Innovation

If licensed, the combination of kaftrio with IVA would become the first medicinal product that targets the underlying cause of CF for use in children (aged 2 year to 5 years) with CF for all patients with at least one F508del mutation, as other licensed treatments have genotype limitations.[5] Some patients that will be eligible for treatment with kaftrio are currently only eligible for symptom management medications that do not treat the underlying disease.[6] Treatment with kaftrio and IVA has been demonstrated to improve Quality of Life (QoL) respiratory scores and lung function in patients with slow damage to the lungs and digestive system, lowing mortality, pulmonary exacerbations, and lung transplants.[7,8]

Regulatory & Development Status

Kaftrio in combination regimen with IVA, has Marketing Authorisation in the UK for the treatment of CF patients aged 6 years and older who have at least one F508del mutation in the CFTR gene.[9]

Kaftrio has the following regulatory designations/ awards:

- Orphan drug in the EU in 2019 for the treatment of cystic fibrosis.[4]
- Breakthrough therapy designation by the US FDA for cystic fibrosis 2019.[10]
- Fast track status by the US FDA for the treatment of cystic fibrosis in 2019.[11]

Patient Group

Disease Area and Clinical Need

Cystic Fibrosis (CF) is an inherited autosomal recessive disorder that is caused by mutations in a gene that makes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is involved in regulating the production of mucus and digestive juices.[4] There are more than 2000 gene variants of the disease that have been identified with the most predominant being the class II mutation in F508del, where the CFTR protein is synthesized but is misfolded hindering its presentation on the cell surface.[3] The genetic

mutation affect the secretion of fluids from the cells in the lungs and glands in the digestive system and pancreas leading to inflammation and long-term infection in the lungs, and to poor growth and nutrition as food cannot be properly absorbed.[4] Symptoms of CF usually start early in childhood and severity gradually increasing through the patient's lifetime with progressive damage to the lungs and digestive system, reducing overall life expectancy. Symptoms include recurring chest infections, wheezing and breathlessness, difficulty gaining weight and growing, jaundice, bowel obstructions in new born babies, osteoporosis, and diabetes.[12]

CF is a rare disease with a prevalence of 1 in 2000 at birth in Northern Europeans and varying prevalence in other populations depending on ethnic composition.[8] In the UK in 2020, 10,837 patients were registered as having CF, of those, 205 were newly diagnosed that year.[13] 33 out of every 100,000 babies born in the UK have CF (2020).[13,14] The median age of death for CF patients that died in 2020 in the UK is 36 years, with 97 deaths reported in 2020. In the five-year period 2016-2020, in the UK, the mean predicted survival age was 50.6 (years).[13] In England (2020-21), there were 7,848 finished consultant episodes (FCE) for CF (ICD-10 code: E84), with 6,762 hospital admissions of which 3,237 were day cases and 34,663 FCE bed days.[15]

Recommended Treatment Options

The aim of cystic fibrosis care is to prevent or limit symptoms and complications of the condition, routine monitoring and annual assessments are crucial in providing effective care; patients aged 1 to 5 years old receive routine reviews every 6 to 8 weeks. General reviews include assessing clinical history, medicine adherence, a physical examination of height and weight, measurement of oxygen saturation, taking respiratory secretion samples, and carrying out lung function tests; annual reviews take a more in-depth look with chest x-rays, blood tests and a physiotherapy assessment.[16] Non-medication therapies include exercise, physiotherapy and breathing exercises to help clear mucus from the lungs, and dietary advise to ensure adequate nutrition, preventing malnutrition and control diabetes symptoms.[17]

There are several types of treatments for CF such as immunomodulatory agents, mucosal agents, in addition to the management/ treatment of various recurrent infections that occur. All mucosal agents use in children 5 years and younger is off label, with human deoxyribonuclease (rhDNase) being the first choice. The only NICE recommended immunomodulatory drug, azithromycin, is also only approved for use in adults, leaving a treatment gap for young children. Flucloxacillin is recommended to be used as a prophylaxis agent against respiratory staphylococcus aureus infection in children with CF from the point of diagnosis up until the age of 3, but this can be continued until age 6; other respiratory infections such as pseudomonas aeruginosa, haemophilus influenzae and non-tuberculous mycobacteria should all be treated with the appropriate antibiotic if they occur.[16]

NHS England clinical commissioning policies also recommend the use of ivacaftor for patients who are aged 4 months and above for the R117H mutation and for 9 named gating mutations when heterozygous in the CFTR gene; and Lumacaftor/ivacaftor for patients who are aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene.[5]

Clinical Trial Information

Trial	NCT04537793, 2020-002251-38; A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple	NCT05153317, 2020-002239-31; A Phase 3 Open-label Study Evaluating the Long-term Safety and Efficacy of

	Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age **Phase III** – Active, not recruiting **Location(s):** UK, USA, Australia, Canada, and Germany **Primary completion date:** May 2022	Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Years and Older **Phase III** – Enrolling by invitation **Location(s):** USA **Primary completion date:** April 2026
Trial Design	Non-randomised, sequential assignment, open-label	Single group assignment, open-label
Population	N= 93; cystic fibrosis patients homozygous for the F508del mutation or heterozygous for F508del and a minimal function (MF) mutation (F/F or F/MF genotypes)	N= 70; cystic fibrosis patients that completed study drug treatment in the parent study (Part B, NCT04537793)
Intervention(s)	Fixed dose combination of ELX, TEZ, and IVA granules for oral administration in the morning, IVA granules for oral administration in the evening.	Fixed dose combination of ELX, TEZ, and IVA granules for oral administration in the morning, IVA granules for oral administration in the evening.
Comparator(s)	No active comparator	No active comparator
Outcome(s)	Primary outcome measures: • Part A: Observed pre-dose concentration (Ctrough) of ELX, TEZ, IVA, and relevant metabolites [Time Frame: From Day 1 through Day 15] • Part A: Safety and tolerability as assessed by number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: From Day 1 up to Day 43] • Part B: Safety and tolerability as assessed by number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: From Day 1 up to Week 28]	Primary outcome measures: • Safety and Tolerability as Assessed by Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

Kaftrio is already marketed in the UK for the treatment of CF in patients; a pack of 56 tablets of Kaftrio (of 50mg, 25mg, 37.5mg strength or 100mg, 50mg, 75mg strength) costs £8346.30 at List Price.[2,18]

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard. Cystic fibrosis (QS168). May 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations. 210508/P. January 2022.
- NHS England. Standard Contract for Cystic fibrosis (children). A01/S/b. July 2018.
- NHS England. Clinical Commissioning Policy: Continuous Aztreonam Lysine for Cystic Fibrosis (all ages). 16001/P. July 2016.
- NHS England. Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. A01/P/b. January 2015.

Other Guidance

- Royal Brompton and Harefield Hospitals (NHS). Clinical guidelines: Care of children with cystic fibrosis. 2020.[19]
- European Cystic Fibrosis Society (ECFS). ECFS best practice guidelines: the 2018 revision. 2018.[20]
- Cystic Fibrosis Foundation (CFF). Clinical practice guidelines from the cystic fibrosis foundation for pre-schoolers with cystic fibrosis. 2016.[21]

Additional Information

Vertex Pharmaceuticals Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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