NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
June 2023

Ivacaftor for cystic fibrosis in infants

Company/Developer	Vertex Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 36073	NICE ID: Not available	UKPS ID: 667875

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Ivacaftor is currently under clinical evaluation to assess its efficacy and safety in infants with cystic fibrosis (CF). CF is a life shortening, inherited condition that occurs due to a faulty gene called cystic fibrosis transmembrane conductance regulator (CFTR). When functioning properly, the CFTR gene should produce a protein which maintains a balance in salt and water that moves into and out of the lungs. If this protein is not produced or does not function typically, then a thick and sticky saliva, called mucus, builds up in multiple organs, including the lungs and causes lung infections. Repeated lung infections and inflammation can cause long term damage and complications in other organs, such as the pancreas. Symptoms include frequent respiratory infections, poor nutritional status and stunted growth. However, there are no approved pharmacological treatment options for this patient population.

Ivacaftor is a new therapeutic agent which increases the activity of the defective CFTR protein making the mucus and digestive juices less thick, thereby helping to relieve symptoms of the disease. It has been proven to improve the activity of the CFTR gene, improve lung function, reduce exacerbations, and improve quality of life. If licensed, ivacaftor will offer a new treatment option for infants who currently have no disease-modifying therapies available.

Proposed Indication

Infants and children who have confirmed diagnosis of cystic fibrosis (CF) by sweat chloride value or CF mutation criteria and at least 1 CFTR gene mutation on at least 1 allele (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H); aged 0 to <24 months.[1]

Technology

Description

Ivacaftor (Kalydeco) is a small-molecule potentiator of the CF transmembrane conductance regulator (CFTR) protein, it increases CFTR channel gating to enhance chloride transport in specified gating mutations with reduced channel-open probability compared to normal CFTR. Ivacaftor also potentiates the channel-open probability of R117H-CFTR, which has both low channel-open probability (gating) and reduced channel current amplitude (conductance).[2]

Ivacaftor is being investigated for safety and efficacy in infants and children with CF under the age of 24 months who have at least one ivacaftor-responsive CFTR gene mutation (NCT02725567 and NCT03277196).[3,4] During the pivotal phase III clinical trial (NCT02725567), ivacaftor was administered orally every 12 hours in doses of 25mg, 50mg or 75mg, depending on the age and weight of the patient over the course of 4 days in part A and 24 weeks in those who took part in part B.[5,6] Recommended doses in infants are: 1 to <2 months (≥3 kg) 5.8mg of ivacaftor every 12 hours, 2 to <4 months (≥3 kg) 13.4mg every 12 hours, 4 to <6 months (≥5 kg) 25mg every 12 hours, 6 months to <6 years (5kg to <7 kg) 25 mg every 12 hours, 6 months to <6 years (7 kg to <14 kg) 50mg every 12 hours, 6 months to <6 years (≥14 kg) 75mg every 12 hours.[7]

Key Innovation

The use of ivacaftor has been shown to both improve CF symptoms and modulate underlying disease pathology. This is achieved by potentiating the channel opening probability (or gating) of CFTR protein in patients with impaired gating mechanisms. This is in contrast to lumacaftor, another CF medication, that functions by preventing misfolding of the CFTR protein and thereby results in increased processing and trafficking of mature protein to the cell surface.[8]

Ivacaftor is the first agent that targets the underlying gene defect in CF.[9] Results from the ARRIVAL study found ivacaftor to be safe and well-tolerated in the studied small cohort of infants aged between 4 to 12 months, with a safety profile comparable to that of older children aged 12 to 24 months and 2 years and older.[5,6] If licensed, ivacaftor will offer a treatment option for treatment for very young patients with CF who currently have no disease-modifying therapies available.

Regulatory & Development Status

Ivacaftor currently has marketing authorisation in the UK, Kalydeco granules are indicated for the treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with CF who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*.[10]

Ivacaftor is currently in phase II clinical development for long QT syndrome.[11]

In July 2008 Ivacaftor received an orphan designation in the EU for CF (EU/3/08/556), now withdrawn from the Community Register of designated orphan medicinal products in July 2022 following the end of market exclusivity.[12]

Patient Group

Disease Area and Clinical Need

CF is a progressive, life-shortening, multisystem disease caused by mutations in the CFTR gene. The mutation results in accumulation of a viscous mucus in multiple organs, including the lungs leading to airway infections, inflammation and long-term lung disease.[6] Lung infections are a cause of significant morbidity for those with CF. The digestive system is also severely impacted, and pancreatic damage, poor nutritional status and growth are common in people with CF.[6] Symptoms can develop very soon after birth but might not appear until early childhood, common symptoms are recurring chest infections, difficulty gaining weight, frequent coughs, diarrhoea and shortness of breath.[13]

Data from the UK Cystic Fibrosis Registry published in 2017 reports UK occurrence of CF as 1 in 2500 live births, with around 200-300 new diagnoses annually.[14] In England, 2021-22, there were 8,127 finished consultant episodes (FCEs) and 6,939 admissions for CF (ICD-10 code E84), which resulted in 35,502 FCE bed days and 3,524 day cases.[15] Between 2021-22 there were 680 recorded primary diagnosis of CF (ICD-10 code E84) in those aged between 0-4 years.[15]

Recommended Treatment Options

There are currently no NICE recommended treatment options for children <24 months who have confirmed diagnosis of cystic fibrosis (CF) by sweat chloride value or CF mutation criteria and at least 1 CFTR gene mutation on at least 1 allele (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H).[16]

Clinical Trial Information

Trial	**ARRIVAL, NCT02725567, EudraCT 2015-001997-16;** A Phase 3, 2 Part, Open-Label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have an Ivacaftor-Responsive CFTR Mutation **Phase III** – Completed **Location(s):** One EU country, UK, USA, Canada and Australia **Study completion date:** June 2022	**NCT03277196;** A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation. **Phase III** - Active, not recruiting. **Location(s):** Two EU countries, UK, USA, Canada and Australia. **Primary completion date:** July 2024
Trial Design	Non-randomised, single group assignment, open-label	Non-randomised, parallel assignment, open-label
Population	N=56 (actual); Infants and children who have confirmed diagnosis of CF by	N=86 (actual); Infants with CF with at least 1 CFTR gene mutation on at least one allele

	sweat chloride value or CF mutation criteria and at least 1 CFTR gene mutation on at least 1 allele (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H); aged 0 to <24 months	who completed part B of NCT02725567; aged 0 to <24 months
Intervention(s)	12 to <24 cohort – Oral ivacaftor 50mg (weight 7 to <14 kg) or 75 mg (weight ≥14 to <25kg) every 12 hours for 4 days in part A and 24 weeks in part B.[6] 6 to <12 months and birth to <6 month cohort – 25mg or 50mg of ivacaftor was delivered orally every 12 hours on the basis of age and weight for 4 days in part A and 24 weeks in part B.[5]	Oral ivacaftor, administered every 12 hours from day 1 through the morning dose of the week 96 visit.
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcome measures for part A and B: • Part A: Safety, as determined by number of subjects with adverse events (AEs), clinically relevant abnormal laboratory values (serum chemistry and hematology), standard 12 lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations [time frame: Day 1 up to Day 70] • Part B: Safety, as determined by number of subjects with adverse events (AEs), clinically relevant abnormal laboratory values (serum chemistry and hematology), standard 12 lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations [time frame: Day 1 up to Week 24] • Part A: Peak concentrations (C3-6h) of ivacaftor, M1 ivacaftor, and M6 ivacaftor [time frame: after 4 days of ivacaftor treatment]	Primary outcome: Safety assessments based on the number of subjects with adverse events (AEs) and serious adverse events (SAEs) [time frame: from baseline through safety follow-up (up to 24 weeks after last dose)] See trial record for full list of all outcomes.

	• Part A: Trough concentrations (Ctrough) of ivacaftor, M1 ivacaftor, and M6 ivacaftor [time frame: after 4 days of ivacaftor treatment] • Part A/B: Safety, as determined by number of subjects with adverse events (AEs), clinically relevant abnormal laboratory values (serum chemistry and hematology), standard 12 lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations [time frame: Day 1 up to Week 24] • Part A/B: Trough concentrations (Ctrough) of ivacaftor, M1 ivacaftor, and M6 ivacaftor [time frame: after 4 days of ivacaftor treatment] See trial record for full list of other outcomes.	
Results (efficacy)	The trial enrolled in sequential age-decreasing cohorts (<24 to 12 months, <12 to 6 months, <6 months to birth) and results for each cohort are reported in separate publications, as follows: 1month <4 month – the mean absolute change from baseline in sweat chloride was -40.3 mmol/L (95% CI: -76.6, -4.1) at week 24.[17] 4 to <12 months - pharmacokinetics was consistent with that in older groups. Sweat chloride concentrations and measures of pancreatic obstruction improved.[5] 12 to <24 months cohort - ivacaftor at doses of 50 mg or 75 mg every 12 hours led to sustained reductions in in sweat chloride, and growth measures were generally well maintained. Reductions in lipase and amylase, a new	-

	observation, along with improvements in fecal elastase-1 and IRT, suggest ivacaftor could potentially preserve pancreatic function if initiated early in life.[6]	
Results (safety)	1month <4 month – one patient discontinued treatment due to transaminase elevations.[17] 4 to <12 months - most adverse events were mild or moderate. In part B, cough was the most common adverse event (n = 10 [58.8%]). Five infants (part A, n = 1 [8.3%]; part B, n = 4 [23.5%]) had serious adverse events, all of which were considered to be not or unlikely related to ivacaftor. No deaths or treatment discontinuations occurred. One infant (5.9%) experienced an alanine transaminase elevation >3 to <5x the upper limit of normal at Week 24. No other adverse trends in laboratory tests, vital signs, or ECG parameters were reported.[5] 12 to <24 months cohort - ivacaftor at doses of 50 mg or 75 mg every 12 hours was generally safe and well tolerated in children 12 to <24 months with CF and a CFTR gating mutation for up to 24 weeks.[6]	-

Estimated Cost

The NHS indicative cost of 28-day ivacaftor supply (25mg, 50mg or 75mg/56 sachets of granules) is £14,000.00 at List Price.[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. 210508P Specialised Commissioning. Updated Commissioning Statement Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutation. January 2022.
- NHS England. 2019/20 NHS Standard Contract for Prescribed Specialised Services Commissioning for Quality and innovation (PSS CQUIN). PSS3 Cystic Fibrosis Supporting Self-care PSS CQUIN indicator. July 2019.
- NHS England. 2017/19 NHS Standard Contract for Prescribed Specialised Services Commissioning for Quality and innovation (PSS CQUIN). Prescribed Services CQUIN Scheme: IM2 Cystic Fibrosis Patient Adherence. September 2017.
- NHS England. A01/P/c. Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis (G551A mutations). July 2015.
- NHS England Commissioning Board. NHSCB/A01/P/b. Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis. March 2012.

Other Guidance

- Royal Brompton hospital. Clinical guidelines: Care of children with cystic fibrosis. 2023.[19]
- Journal of Cystic Fibrosis. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. 2022.[20]
- The Cystic Fibrosis Foundation. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. 2020.[21]
- The European CF Society. ECFS best practice guidelines: the 2018 revision. 2018.[22]
- The European CF Society. ECFS Standards of Care. 2014.[23]

Additional Information

Ivacaftor is available to eligible patients aged four months and older via a managed access agreement between NHS England, NHS Improvement and Vertex.[24]

References

1 *A Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have an Ivacaftor-Responsive CFTR Mutation*. *Trial ID: NCT02725567*. 2016. Status: Completed. Available from: https://ClinicalTrials.gov/show/NCT02725567 [Accessed 03 May 2023].

2 Electronic medicines compendium (emc). *Kalydeco 50 mg granules in sachet: 5.1 Pharmacodynamic properties*. 2021. Available from: https://www.medicines.org.uk/emc/product/1954/smpc#gref [Accessed 05 April 2023].

3 ClinicalTrials.gov. *A Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have an Ivacaftor-Responsive CFTR Mutation*. *Trial ID: NCT02725567*. 2022. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02725567?term=NCT02725567&draw=2&rank=1 [Accessed 15 May 2022].

4 ClinicalTrials.gov. *A Study to Evaluate the Safety of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation*. *Trial ID: NCT03277196*. 2017. Status:

Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03277196?term=NCT03277196&draw=2&rank=1 [Accessed 15 May 2023].

5 Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, et al. Ivacaftor in Infants Aged 4 to <12 Months with Cystic Fibrosis and a Gating Mutation. Results of a Two-Part Phase 3 Clinical Trial. *American Journal of Respiratory and Critical Care Medicine*. 2021;203(5):585-93. https://doi.org/10.1164/rccm.202008-3177OC

6 Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *The Lancet Respiratory Medicine*. 2018;6(7):545-53. https://doi.org/10.1016/S2213-2600(18)30202-9.

7 Vertex. *Highlights of prescribing information*. 2023. Available from: https://www.kalydecohcp.com/trial-8# [Accessed 17 May 2023].

8 Drugbank online. *Ivacaftor*. 2012. Available from: https://go.drugbank.com/drugs/DB08820 [Accessed 09 June 2023].

9 Condren ME, Bradshaw MD. Ivacaftor: a novel gene-based therapeutic approach for cystic fibrosis. *J Pediatr Pharmacol Ther*. 2013;18(1):8-13. Available from: https://doi.org/10.5863/1551-6776-18.1.8.

10 Electronic medicines compendium (EMC). *Kalydeco 50 mg granules in sachet*. 2021. Available from: https://www.medicines.org.uk/emc/product/1954/smpc#gref [Accessed 12 May 2023].

11 ClinicalTrials.gov. *14 Studies found for: Ivacaftor, Kalydeco | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation, Unknown status Studies | Phase 2, 3 Also searched for Ivacaftor and VX-770*. Available from: https://clinicaltrials.gov/ct2/results?term=Ivacaftor%2C+Kalydeco&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&recrs=m&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 05 April 2023].

12 European Medicines Agency (EMA). *EU/3/08/556: Orphan designation for the treatment of cystic fibrosis*. 2022. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-08-556 [Accessed 17 May 2023].

13 National Health Service (NHS). *Overview: Cystic fibrosis*. 2021. Available from: https://www.nhs.uk/conditions/cystic-fibrosis/ [Accessed 03 May 2023].

14 Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, et al. Data Resource Profile: The UK Cystic Fibrosis Registry. *International Journal of Epidemiology*. 2017;47(1):9-10e. https://doi.org/10.1093/ije/dyx196

15 NHS75 Digital. *Hospital Admitted Patient Care Activity, 2021-22: Diagnosis* 2020-21. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 03 May 2023].

16 National Instititute for health and Care Excellence (NICE). *Cystic fibrosis Products. A list of all our products on cystic fibrosis*. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases/cystic-fibrosis/products?ProductType=Guidance&Status=Published [Accessed 09 June 2023].

17 Vertex. *Clinical Trials for Patients Age 1 Month to <2 Years TRIAL 8 (ARRIVAL): KALYDECO® (ivacaftor) in patients with CF age 1 month to <2 years*. Available from: https://www.kalydecohcp.com/trial-8 [Accessed 17 May 2023].

18 British National Formulary (BNF). *Ivacaftor Medicincal forms*. Available from: https://bnf.nice.org.uk/drugs/ivacaftor/medicinal-forms/ [Accessed 04 April 2023].

19 Royal Brompton hospital. *Clinical guidelines: Care of children with cystic fibrosis, 2023*. 2023. Available from: https://www.rbht.nhs.uk/childrencf [Accessed 04 April 2023].

20 Southern KW, Castellani C, Lammertyn E, Smyth A, VanDevanter D, van Koningsbruggen-Rietschel S, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *J Cyst Fibros*. 2023;22(1):17-30. Available from: https://doi.org/10.1016/j.jcf.2022.10.002.

21 Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. *J Cyst Fibros*. 2020;19(3):344-54. Available from: https://doi.org/10.1016/j.jcf.2020.02.015.

22 Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros*. 2018;17(2):153-78. Available from: https://doi.org/10.1016/j.jcf.2018.02.006.

23 The European CF Society. *ECFS Standards of Care Available in Open Access*. 2014. Available from: https://www.ecfs.eu/news/ecfs-standards-care-available-open-access [Accessed 04 April 2023].

24 National Institute for Health and Care Excellence (NICE). *Data collection agreement*. 2019. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement#parties-to-this-agreement [Accessed 12 June 2023].

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.