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Lumacaftor and ivacaftor (Orkambi) for cystic fibrosis homozygous for the F508del CFTR mutation in patients aged 2-5 years old

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LAY SUMMARY

Cystic fibrosis is an inherited disease that has severe effects on the lungs and the digestive system. It affects the cells that produce mucus and digestive juices. In cystic fibrosis, the secretions become thick and cause blockage within the tissues and organs (mostly within the lungs). Build-up of thick and sticky secretions in the lungs causes inflammation and long-term infection. In the gut, blockage of the tubes from the pancreas slows down the digestion of food and causes poor growth. People with cystic fibrosis are also at a higher risk of developing a number of related conditions such as diabetes, thin, weakened bones (osteoporosis) and liver problems, leading to a poor quality of life.

Lumacaftor and ivacaftor (Orkambi) is a medicine used to treat cystic fibrosis in patients aged 2 to 5 years who have a genetic mutation called the F508del mutation. This mutation affects the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR) which is involved in regulating the production of mucus and digestive juices. Orkambi is used in patients who have inherited the mutation from both parents and therefore have the mutation in both copies of the CFTR gene. Orkambi is taken orally as tablets twice a day. It offers a new treatment option for patients with cystic fibrosis with the advantage of targeting the actual disease process rather than just the symptoms.

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TARGET GROUP

Cystic fibrosis in patients aged 2 to 5 years homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

TECHNOLOGY

DESCRIPTION

Lumacaftor with ivacaftor (Orkambi; lumacaftor/ivacaftor) is a fixed dose combination of two systemic protein modulators. Lumacaftor (VX809) is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor (VX770) is a CFTR potentiator. The combined effect of lumacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. The exact mechanisms by which lumacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.[1] It is formulated as film coated tablets for oral route of administration.[2]

Lumacaftor/ivacaftor is in pre-registration for the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years old who are homozygous for the F508del mutation in the CFTR gene (NCT02797132).[3] Patients <14kg are administered two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) orally every 12 hours. For those ≥14kg, patients are administered two tablets (lumacaftor 150 mg/ivacaftor 188 mg) orally every 12 hours. Treatment duration was not reported on the trial registry.[3]

Lumacaftor/ivacaftor are licensed as a fixed-dose combination for use in patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene (two lumacaftor 100 mg/ivacaftor 125mg dose every 12 hours),[1] and for patients aged 12 years and older (two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours).[4] Very common adverse reactions identified from the 24-week, placebo-controlled phase III study in patients 6 to 11 years (NCT01897233) include nasopharyngitis, headache, dizziness, nasal congestion, dyspnoea, productive cough, sputum increased, (upper) abdominal pain, diarrhoea, nausea and bacteria in sputum.[1]

INNOVATION and/or ADVANTAGES

Lumacaftor/ivacaftor has been shown to improve lung function and lung ventilation in patients with CF aged 6 years and above due to combined actions of the two active substances. One of the active substances, lumacaftor, increases the number of CFTR protein on the cell surface. The other, ivacaftor, increases the activity of the defective CFTR protein. These actions make mucus and digestive juices less thick.[5]

When investigated in clinical trials for children aged 2 to 5 years old, lumacaftor/ivacaftor was generally well tolerated and indicated that there were no new safety concerns compared to the aged 6 to 11 years population.[6]

DEVELOPER

Vertex Pharmaceuticals Inc

PATIENT GROUP

BACKGROUND

Cystic fibrosis (CF) is an autosomal recessive, progressive, and usually fatal genetic disease. CF is most common in the Caucasian population, and is considered an orphan disease.[7] Lack of properly functioning CFTR ion channel is responsible for the clinical sequelae of CF. This includes malabsorption of nutrients and the inability to mobilize tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are over 2,000 mutations in the CFTR gene, some of which, when present in one or both CFTR alleles, result in the clinical constellation that is CF.[8]

Symptoms of CF tend to start in early childhood, although they can sometimes develop very soon after birth, or may not be obvious until adulthood. Some of the main symptoms of CF can include:

- recurring chest infections
- difficulty putting on weight
- frequent, wet-sounding coughs
- diarrhoea
- occasional wheezing and shortness of breath.

People with the condition can also develop a number of related conditions, including diabetes, thin, weakened bones (osteoporosis), liver problems, and fertility problems, especially in men.[9, 10]

CF is a progressive condition, which means it tends to get worse over time. Eventually the condition can be fatal if it leads to a serious infection or the lungs stop working properly.[9]

The outlook for CF has improved considerably in recent years because of advancements in treatment, although most people with the condition will have a shorter-than-average life expectancy. Currently, about half of the people with CF will live past the age of 40. Children born with the condition nowadays are likely to live longer.[9]

CLINICAL NEED and BURDEN OF DISEASE

The incidence of CF varies between populations: the condition is considerably less common in Asian and African populations than in the white populations of Europe and North America, with variations within each country. The exact prevalence in Europe is unknown, but estimates range between 1 in 8,000 and 1 in 10,000 individuals.[7]

In the UK, CF is estimated to occur in around 1 in 2,500 live births with approximately 200 to 300 new diagnosis annually.[11] The latest UK Cystic Fibrosis Registry indicates a total of 10,461 people living with CF in the UK in 2016, of which 247 were newly diagnosed.[12] Approximately 40% are children under 16 years of age, of which 20.6% are between 4 and 11 years.[12]

Median survival ages for people with one or two copies of F508del, diagnosed at birth, were 46 years for males and 41 for females. This represents around 95% of the UK CF population. For those with two

copies of F508del (around 40-50% of that group), the median survival age for those who live to age 30 rises to 52 for men and 49 for females.[13]

The 2016/17 Hospital Episodes Statistics for England recorded 16,287 finished consultant episodes (FCE), 13,879 admissions and 5,435 days cases for cystic fibrosis (ICD-10 code: E.84).[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation (GID-TA10277). 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 clinical guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard in development. Cystic fibrosis (GID-QS10052). Publication anticipated May 2018.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Respiratory Services: Cystic Fibrosis Children. A01/S/b.
- NHS England. Clinical Commissioning Policy Statement: Ivacaftor for children aged 2-5 years with cystic fibrosis (named mutations). 16049/P. December 2016.

OTHER GUIDANCE

- Standard for the clinical care of children and adults with cystic fibrosis in the UK. Second ed. December 2011.[15]

CURRENT TREATMENT OPTIONS

There are currently no treatment options available that specifically target the F508del mutation. Current treatments for CF generally manage the complications rather than the cause of the disease.[16]

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) and
- lung transplantation.[16]

NICE technology appraisal guidance 266 recommends mannitol dry powder for inhalation as an option for treating CF in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and, whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate.[16, 17]

EFFICACY and SAFETY		
Trial	NCT02797132, EudraCT 2016-001004-33; children aged 2-5 years; lumacaftor/ivacaftor fixed-dose combination (experimental doses based on participant weight); phase III	NCT03125395; children aged 2 years and older; lumacaftor/ivacaftor fixed-dose combination (experimental doses based on participant weight) vs observational cohort; phase III extension
Sponsor	Vertex Pharmaceuticals Inc	Vertex Pharmaceuticals Inc
Status	Completed	Ongoing
Source of Information	Trial registry,[3] Company report[18]	Trial registry[19]
Location	USA and Canada	USA and Canada
Design	Non-randomised, open-label, uncontrolled study	Non-randomised, open-label, uncontrolled study
Participants	n=60; aged 2 to 5 years old; cystic fibrosis (CF) in patients homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene who weigh ≥8 kilogram (kg).	n=57; aged ≥2 years old; cystic fibrosis in patients homozygous for the F508del mutation in the CFTR gene who completed 24 weeks of lumacaftor/ivacaftor treatment and the safety follow-up visit in study VX15-809-115 part B (study 115B, NCT02797132).
Schedule	Patients <14kg received two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) orally every 12 hours. Patients ≥14kg received two tablets (lumacaftor 150 mg/ivacaftor 188 mg) orally every 12 hours. The same two experimental arms were further advanced into Part B of the study where additional primary and secondary outcomes were measured for a total of 24 weeks.	Patients <6 years of age and <14 kg at enrolment received two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) orally every 12 hours. Patients <6 years of age and ≥14 kg at enrolment received two tablets (each containing lumacaftor 150 mg/ivacaftor 188 mg) orally every 12 hours. Patients ≥6 years of age at enrolment, regardless of weight received two tablets (each containing lumacaftor 200 mg/ivacaftor 250 mg) orally every 12 hours.
Follow-up	Subjects who completed 24 weeks of the lumacaftor/ivacaftor treatment and safety follow up were eligible to enrol in an extension study.	From baseline through safety follow-up (up to 98 weeks)
Primary Outcomes	Part A: Pharmacokinetic (PK) parameters of lumacaftor and ivacaftor: estimated peak	Safety and tolerability assessments based on the number of subjects with adverse events and serious adverse

	concentrations [Time Frame: up to 15 Days] Part A: Pharmacokinetic parameters of lumacaftor and ivacaftor: estimated trough concentrations [Time Frame: up to 15 Days] Part B: Safety and Tolerability assessments as determined by number of subjects with adverse events and serious adverse event [Time Frame: Baseline up to 28 days after last dose (up to 28 weeks)]	event [Time Frame: From baseline through safety follow-up (up to 98 weeks).]
Secondary Outcomes	Part A: PK parameters of lumacaftor and ivacaftor metabolites: estimated peak concentrations (Cmax) of lumacaftor and ivacaftor metabolites [Time Frame: up to 15 days] Part A: PK parameters of lumacaftor and ivacaftor metabolites: estimated trough concentrations (Ctrough) of lumacaftor and ivacaftor metabolites [Time Frame: up to 15 days] Part A: Safety and Tolerability assessments as determined by number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Baseline up to 10 +/- 3 days after the last dose (up to 25 +/- 3 days)] Part B: Absolute change from baseline in sweat chloride level [Time Frame: Baseline, Week 24] Part B: Absolute change from baseline in body mass index (BMI) and BMI for age z score [Time Frame: Baseline, Week 24] Part B: Absolute change from baseline in weight and weight for age z score [Time Frame: Baseline, Week 24] Part B: Absolute change from baseline in stature and stature for age z score [Time Frame: Baseline, Week 24]	Absolute change from baseline in sweat chloride [Time Frame: From baseline through 96 weeks.] Sweat samples will be collected using an approved collection device. Absolute change in sweat chloride will be reported. Absolute change from baseline in body mass index (BMI) [Time Frame: From baseline through 96 weeks.] BMI is defined as weight in kilogram (kg) divided by height*height in square meter (m^2). Absolute change in BMI will be reported. Absolute change from baseline in BMI-for-age Z-score [Time Frame: From baseline through 96 weeks.] BMI is defined as weight in kg divided by height*height in m^2. Z-score is a statistical measure to evaluate how a single data point compares to a standard. Absolute change in BMI-for-age Z-score will be reported. Absolute change from baseline in weight [Time Frame: From baseline through 96 weeks.] Weight will be measured in kg and absolute change will be reported. Absolute change from baseline in weight-for-age Z-score [Time Frame: From baseline through 96 weeks.] Weight will be measured in kg. Z-score is a statistical measure to evaluate how

	Part B: Absolute change from baseline in lung clearance index (LCI)2.5 [Time Frame: Baseline, Week 24] Part B: Absolute change from baseline in LCI5.0 [Time Frame: Baseline, Week 24] Part B: Time-to-first pulmonary exacerbation [Time Frame: through Week 24] Part B: Number of pulmonary exacerbations [Time Frame: through Week 24] Part B: Number of CF-related hospitalizations [Time Frame: through Week 24] Part B: Absolute change from Baseline in fecal elastase-1 (FE-1) levels [Time Frame: Baseline, Week 24] Part B: Absolute change in serum levels of immunoreactive trypsinogen (IRT) [Time Frame: from baseline through Week 24] Part B: Changes in sputum microbiology cultures [Time Frame: Baseline, Week 24] Part B: Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) [Time Frame: Baseline, Week 24] Part B: Acceptability/palatability of lumacaftor/ivacaftor granules measured using hedonic scale [Time Frame: Day 1] Part B: PK parameters of lumacaftor, ivacaftor, and their respective metabolites: estimated trough concentrations (Ctrough) of lumacaftor and ivacaftor and their metabolites [Time Frame: up to 24 weeks]	a single data point compares to a standard. Absolute change in weight-for-age Z-score will be reported. Absolute change from baseline in stature [Time Frame: From baseline through 96 weeks.] Stature (height) will be measured in centimeter (cm) and absolute change will be reported. Absolute change from baseline in stature-for-age Z-score [Time Frame: From baseline through 96 weeks.] Stature (height) will be measured in cm. Z-score is a statistical measure to evaluate how a single data point compares to a standard. Absolute change in stature-for-age Z-score will be reported. Time-to-first pulmonary exacerbation [Time Frame: From baseline through 96 weeks.] Pulmonary exacerbation refers to the intermittent episodes of acute decline of lung function and worsening of symptoms. Time to first pulmonary exacerbation will be reported. Number of pulmonary exacerbations [Time Frame: From baseline through 96 weeks.] Pulmonary exacerbation refers to the intermittent episodes of acute decline of lung function and worsening of symptoms. Number of pulmonary exacerbations during the study will be reported. Number of CF-related hospitalizations [Time Frame: From baseline through 96 weeks.] Number of hospitalizations due to CF during the study will be reported. Absolute change from baseline in fecal elastase-1 (FE-1) levels [Time Frame: From baseline through 96 weeks.] Absolute change in FE-1 levels will be reported.

		Absolute change from baseline in serum levels of immunoreactive trypsinogen (IRT) [Time Frame: From baseline through 96 weeks.] Absolute change in IRT serum levels will be reported. Change from baseline in sputum microbiology cultures [Time Frame: From baseline through 96 weeks.] Change in sputum microbiology cultures will be reported. Absolute change from baseline in lung clearance index (LCI)2.5 [Time Frame: From baseline through 96 weeks.] LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques. LCI 2.5 will be defined as the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. Absolute change in LCI2.5 will be reported. Absolute change from baseline in LCI5.0 [Time Frame: From baseline through 96 weeks.] LCI is a measure of ventilation inhomogeneity that is based on tidal breathing techniques. LCI 5.0 will be defined as the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value. Absolute change in LCI5.0 will be reported.
Key Results	The study met its primaryendpoint of safety showing that lumacaftor/ivacaftor was generally well tolerated and there were no new safety concerns compared to prior studies of lumacaftor/ivacaftor in ages 6 through 11. Secondary endpoints showed decreases in sweat chloride and improvements in nutritional status as measured by change in weight (weight-for-age z score) and body mass index (BMI-for-age z score).[18]	-
Adverse effects (AEs)	Not reported	-

Expected reporting date	-	Primary completion date is reported as July 2019

ESTIMATED COST and IMPACT

COST

Lumacaftor/ivacaftor is already marketed in the UK for the treatment of cystic fibrosis in patients who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; a packet of 112 tablets (200mg/125mg tablets) costs £8,000.00.[2]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduced use of secondary care/specialist services, reduced need for interventional procedures*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

No information was received from Vertex Pharmaceuticals.

Vertex Pharmaceuticals 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.

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