Lumacaftor and ivacaftor combination therapy for cystic fibrosis – first line

SUMMARY

Lumacaftor and ivacaftor combination therapy is intended for first line use in patients aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del-CFTR mutation. If licensed, this combination therapy will offer an additional treatment option for this patient group, who currently have no therapies available that target the F508del-CFTR mutation. Lumacaftor and ivacaftor (Kalydeco) are systemic protein modulators. Lumacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor is a CFTR potentiator. Ivacaftor 150mg is currently licensed in the EU for the treatment of CF in patients age 6 years and older who have a G551D mutation in the CFTR gene.

CF is an autosomal recessive disease caused by mutations in the CFTR gene. It affects over 8,500 children and young adults in the UK and has an incidence of 1 in 2,500 live births. The prevalence of CF in the UK is 1.37 per 10,000 population. There are currently 10,078 people with CF on the UK CF registry; 274 of these were newly registered in 2012, of which 157 were diagnosed on newborn screening. Over 1,000 disease-causing alleles within the CFTR gene have been identified. The most common mutation is the F508del-mutation which is present on around 67% of CF chromosomes worldwide. Around 8,500 (97%) patients on the CF registry have been genotyped of whom 4,371 (51.7%) are homozygous for the F508del-CFTR mutation.

There is currently no treatment available that specifically targets the F508del-CFTR mutation and current treatments generally address the complications rather than cause of the disease. Lumacaftor and ivacaftor combination therapy is in three phase III clinical trials comparing its effect on change in lung function testing and safety against treatment with placebo. These trials are expected to complete by Q3 2017.
TARGET GROUP

- Cystic fibrosis: patients aged 12 years and older; homozygous for the F508del-CFTR mutation – first line.

TECHNOLOGY

DESCRIPTION

Lumacaftor (VX809) and ivacaftor (Kalydeco, VX770) are systemic protein modulators. Lumacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor is a CFTR potentiator. Lumacaftor and ivacaftor combination therapy is intended for the first line use of patients aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del-CFTR mutation. In the phase III clinical trial lumacaftor is administered orally at 600mg once daily or 400mg once every 12 hours, and ivacaftor is administered orally at 250mg once every 12 hours, both on a continuing basis.

Ivacaftor 150mg is licensed in the EU for the treatment of CF in patients aged 6 years and older who have a G551D mutation in the CFTR gene. Common adverse effects include: nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, abdominal pain, rash, and diarrhoea. Lumacaftor does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, lumacaftor and ivacaftor combination therapy will offer an additional treatment option for this patient group, who currently have no therapies available that target the F508del-CFTR mutation.

DEVELOPER

Vertex Pharmaceuticals UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

The individual compounds ivacaftor and lumacaftor have designated orphan drug status in the EU.

PATIENT GROUP

BACKGROUND

CF is an autosomal recessive disease caused by mutations in the CFTR gene. This causes failure of chloride secretion and sodium hyperabsorption at the apical airway surface, which leads to dehydration of the airway surface fluid layer and impaired mucociliary clearance in the lungs, pancreas, liver, intestine and reproductive tract, and an increase in the salt content in sweat gland secretions.
People with CF are prone to lung infections by a range of pathogens, including *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Burkholderia cepacia*. These bacteria thrive in the altered hyperviscous mucus of people with CF, who may then develop chronic infection where bacterial microenvironments known as biofilms are formed, which are difficult for immune cells and antibiotics to penetrate. Bacterial infection is rarely eradicated once chronic infection has developed. Chronic inflammation and progressive lung destruction from chronic infection can lead to bronchiectasis, altered pulmonary function and respiratory failure. While CF is a multi-system disease, the primary cause of death in people with CF is respiratory failure resulting from chronic pulmonary infection.

The development of chronic *P. aeruginosa* infection is associated with increased morbidity and mortality and a lower quality of life. While eradication is attempted in those who develop acute *P. aeruginosa* infection, it is not always successful. Expert opinion indicates that it may simply delay the onset of chronic infection. Of the 30-40% of patients who remain *P. aeruginosa* free, many have never developed acute *P. aeruginosa*.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- Improving quality of life for people with long term conditions.

**CLINICAL NEED and BURDEN OF DISEASE**

CF affects over 8,500 children and young adults in the UK and has an incidence of 1 in 2,500 live births. The prevalence of CF in the UK is 1.37 per 10,000 population. CF is much less common in people from Black Caribbean, Black African and Asian ethnic groups. There are currently 10,078 people with CF on the UK CF registry; 274 of these were newly registered in 2012, of which 157 were diagnosed on newborn screening. Over 57% of the patients registered are over 16 and there are now over 800 people with CF on the registry aged over 40. Over 1,000 disease-causing alleles within the *CFTR* gene have been identified. The most common mutation is the F508del-mutation which is present on around 67% of CF chromosomes worldwide. Around 8,500 (97%) patients on the CF registry have been genotyped of whom 4,371 (51.7%) are homozygous for the F508del-CFTR mutation.

CF is a progressive condition that reduces life expectancy. In 2012, the CF registry recorded 106 deaths in UK patients; the median age at death was 28 years. However, prognosis is improving with newborn screening, better disease management and symptomatic treatments now available. Around half of the current CF population are expected to have a life expectancy of over 40 years.

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*a* Expert personal communication.

*b* Information provided by company.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance

• Cystic Fibrosis Trust. Antibiotic treatment for cystic fibrosis. 2009.
• Clinical practice guidelines on growth and nutrition subcommittee, ad hoc working group; Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: Results of a systematic review. 2008.
• Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. 2007.

CURRENT TREATMENT OPTIONS

There is currently no treatment available that specifically targets the F508del-CFTR mutation and current treatments generally address the complications rather than cause of the disease. CF treatment can be time-consuming for the patient, with administration of nebulised antibiotics taking up to an hour each day during good health and longer during periods of ill health. The disease also impacts upon carers and needs a considerable commitment of healthcare resources.

Treatments can be broadly classified as nutritional repletion (e.g. pancreatic enzyme supplementation and nutritional supplementation), relief of airway obstruction (e.g. physiotherapy, drugs to improve sputum clearance such as rhDNase; hypertonic saline;
Management of *P. aeruginosa* lung infection in CF involves treatment with antibiotics, which may be given in hospital, at home, or in a combination of these settings. The aims of antibiotic treatment are three-fold: firstly to eradicate intermittent acute *P. aeruginosa* lung infections; secondly to suppress *P. aeruginosa* (with long-term treatment) in patients who have become chronically infected; and thirdly to treat acute exacerbations in patients chronically infected with *P. aeruginosa*. Treatment also aims to maintain lung function and quality of life. Current treatment options include the use of inhaled antibiotics effective against *P. aeruginosa* (such as nebulised colistimethate sodium, tobramycin or aztreonam) and oral or intravenous antibiotics to eradicate initial or intermittent *P. aeruginosa* colonisation or acute exacerbations of chronic infection. Azithromycin may be given in combination with these antibiotics to act on the biofilms but its mechanisms of action are not fully understood.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>TRANSPORT, NCT01807949, VX12-809-104; lumacaftor and ivacaftor vs placebo; phase III.</th>
<th>TRAFFIC, NCT01807923, VX12-809-103; lumacaftor and ivacaftor vs placebo; phase III.</th>
<th>NCT01931839, VX12-809-105; phase III extension.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Vertex Pharmaceuticals Inc.</td>
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<tr>
<td>Source of information</td>
<td>Trials registry¹.</td>
<td>Trials registry².</td>
<td>Trials registry²².</td>
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<tr>
<td>Location</td>
<td>EU (inc UK), USA and Canada and other countries.</td>
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<tr>
<td>Participants</td>
<td>n=563 (planned); aged 12-65 years; CF; homozygous for F508del-CFTR mutation.</td>
<td>n=559 (planned); aged 12-65 years; CF; homozygous for F508del-CFTR mutation.</td>
<td>n=1,122 (planned); aged 12-65 years; CF; homozygous or heterozygous for F508del-CFTR mutation; participants from NCT01807949, NCT01807923 and NCT01225211.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to lumacaftor 600mg oral once daily, in combination with ivacaftor 250mg oral once every 12 hours; or lumacaftor 400mg oral, in combination with ivacaftor 250mg oral, both once every 12 hours; or placebo.</td>
<td>Randomised to lumacaftor 600mg oral once daily, in combination with ivacaftor 250mg oral once every 12 hours; or lumacaftor 400mg oral twice daily, in combination with ivacaftor 250mg oral once every 12 hours; or placebo.</td>
<td>Participants receive: Part A treatment, arm 1: Lumacaftor 600mg oral once daily, in combination with ivacaftor 250mg oral once every 12 hours. Part A treatment, arm 2: Lumacaftor 400mg oral, in...</td>
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</table>

¹ Expert personal communication.
² Participants entering part A completed 24 weeks of lumacaftor/ivacaftor in NCT01807949 or NCT01807923 and elect to enrol in part A treatment arm.
| Follow-up | Part A observational arm:
long-term follow-up. |
| Part B treatment, arm 3e:
Lumacaftor 400mg oral, in combination with ivacaftor 250mg oral; both once every 12 hours. |
| Part A observational arm:
long-term follow-up. |
| Primary outcome/s | Safety. |
| Secondary outcome/s | Safety. |
| Expected reporting date | Primary completion date reported as May 2017. |

**Trial**

NCT01225211, VX09-809-102, 2010-020413-90; lumacaftor alone or in combination with ivacaftor; phase II (cohorts 2 and 3).

**Sponsor**

Vertex Pharmaceuticals Inc.

**Status**

Ongoing.

**Source of information**

Trials registry, press release.

**Location**

USA, Australia, Belgium, Germany and New Zealand.

**Design**

Randomised, placebo-controlled.

**Participants**

n=293 (planned); aged 18 years and older; CF; homozygous or heterozygous for the F580del-CFTR mutation.

**Schedule**

Randomised to:

- **Arm 1 (homozygous subjects):** lumacaftor 400mg oral once daily for 28 days; on days 29-56 participants receive lumacaftor 400mg oral, once daily; in combination with ivacaftor 250mg oral, once every 12 hours.
- **Arm 2 (homozygous and heterozygous subjects):** placebo oral, once daily/once every 12 hours for 21 days.

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\(^{e}\) Participants entering part B completed 56 days of lumacaftor/ivacaftor in NCT01225211 and elect to enrol in part B treatment arm.

\(^{f}\) Participants entering part A observational arm completed 24 weeks of lumacaftor/ivacaftor in NCT01807949 or NCT01807923 but do not elect to enrol in the part A treatment arms or do not qualify for enrolment in Part A treatment arms.

\(^{g}\) This is the volume that has been exhaled at the end of the first second of forced expiration.
Arm 3 (homozygous subjects): lumacaftor 200mg oral, once daily for 28 days; on days 29-56 participants receive lumacaftor 200mg oral, once daily, in combination with ivacaftor 250mg oral, once every 12 hours.

Arm 4 (homozygous subjects): lumacaftor 400mg oral, once every 12 hours for 28 days; on days 29-56 participants receive lumacaftor 400mg oral, in combination with ivacaftor 250mg oral, both once every 12 hours.

Arm 5 (homozygous subjects): lumacaftor 600mg oral, once daily for 28 days; on days 29-56 participants receive lumacaftor 600mg oral, once daily in combination with ivacaftor 250mg oral, once every 12 hours.

Arm 6 (heterozygous subjects): lumacaftor 600mg oral, once daily for 28 days; on days 29-56 participants receive lumacaftor 600mg oral, once daily and ivacaftor 250mg oral, once every 12 hours.

Follow-up
Active treatment period up to 56 days.

Primary outcome/s
Change in sweat chloride on days 14-21.

Secondary outcome/s
Change in FEV1 on days 1, 7 and 14; safety.

Key results
For lumacaftor 600mg alone and in combination with ivacaftor vs placebo respectively: changes in lung function day 0-28, -2.0 (p=0.36) vs -0.9 (p=0.54); changes in lung function day 28-56, +8.6 (p<0.001) vs -2.5 (p=0.08); ≥ 5 percentage point absolute improvement FEV1, day 0-28, 10% vs 13%; ≥ 5 percentage point absolute improvement FEV1, day 28-56, 55% vs 9.5%; ≥ 10 percentage point absolute improvement FEV1, day 0-28, 5% vs 4.3%; ≥ 10 percentage point absolute improvement FEV1, day 28-56, 25% vs 0%.

Adverse effects (AEs)
Lumacaftor alone and in combination with ivacaftor was generally well tolerated. The most common AEs were respiratory in nature. Most AEs were mild to moderate in severity and similar between treatment and placebo groups.

Expected reporting date
Primary completion date reported as Mar 2014.

ESTIMATED COST and IMPACT

COST

The cost of lumacaftor and ivacaftor combination therapy is not yet known. Ivacaftor (Kalydeco) is already marketed in the UK for CF in patients age 6 years and older who have a G551D mutation in the CFTR gene; a pack of 56 x 150mg tablets costs £14,00025.

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: oral therapy with potential to reduce complications.
□ Re-organisation of existing services □ Need for new services
□ Other: □ None identified
Impact on Costs and Other Resource Use

- Increased drug treatment costs: 
  *New combination therapy.*

- Reduced drug treatment costs: 
  *Expert opinion indicates that if lumacaftor and ivacator combination therapy works well then it may reduce other treatment costs; younger patients may not develop progressive disease, and there is some evidence that they may also lose their chronic P. aeruginosa infection.*

- Other increase in costs:

- Other reduction in costs:

- Other:

Other Issues

- Clinical uncertainty or other research question identified: 
  *According to expert opinion the preliminary data for this combination therapy suggests that there will be less of a corrective effect on the F508del-CFTR mutation than seen with ivacator for the G551D-CFTR mutation; which subsequently may result in this treatment becoming an add-on to existing therapy for CF.*

- None identified

REFERENCES


10 Flume PA, Mogayzel PJ, Robinson KA et al. Clinical Practice Guidelines for Pulmonary Therapies Committee; Cystic Fibrosis Foundation Pulmonary Therapies Committee. Cystic Fibrosis

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h Expert personal communication.


24 Final data from phase 2 combination study of VX-809 and KALYDECO™ (ivacaftor) showed statistically significant improvements in lung function in people with cystic fibrosis who have two copies of the F508del Mutation. Vertex Pharmaceuticals. June 2012.