

THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

New drug for cystic fibrosis: Regulatory approval, clinical uncertainty?

A new drug for cystic fibrosis (CF) that combines lumacaftor and ivacaftor (Orkambi), was approved by Health Canada (HC) in 2016 to treat people age 12 and older with the most frequent CF genetic mutation: homozygous F508 deletion of the cystic fibrosis transmembrane regulator (CFTR) gene. This affects 50% of the Canadian CF population.

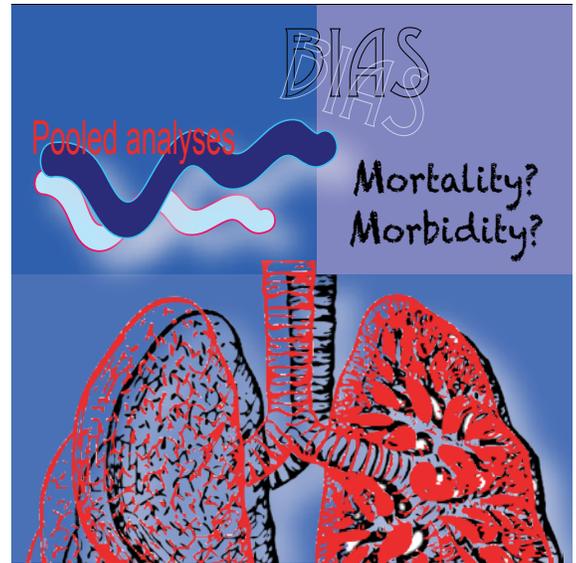
In CF, mucus membranes do not release an adequate amount of moisture, therefore respiratory and other secretions are thick and sticky. This leads to an increase in respiratory infections, scarring, and deterioration in lung function, as well as pancreatic insufficiency and inadequate nutrition.

Current therapy includes both pharmacotherapy (antibiotics, mucolytics, pancreatic enzymes) and physiotherapy. These therapies are critical to reducing the frequency and severity of lung infections and slowing the deterioration in lung function. As a result of these therapies, Canadian CF patients now have a median survival of over age 50.¹

Lumacaftor/ivacaftor (LUM/IVA) attempts to modulate the cellular dysfunction caused by a specific gene mutation. Lumacaftor is understood to 'correct' the misfolding of the CFTR protein caused by the F508del gene mutation, while ivacaftor is understood to 'potentiate' a gating mechanism at the cell surface.

The basis for regulatory approval

Regulatory approval² was based on the findings of two studies that randomized 750 subjects, age 12 years and older, to placebo or the recommended dose of LUM 400 mg / IVA 250 mg administered every 12 hours for 24 weeks.^{3,4} Participants were eligible for enrolment if they had stable mild to moderate disease. Both study groups received current therapy as per their usual routine or as needed to treat pulmonary exacerbations.



The primary efficacy outcome was the average change in the 'percent predicted forced expiratory volume in the first second of expiration' (ppFEV₁) as measured by spirometry at 16 and 24 weeks. The ppFEV₁ improvements of 2.6% and 3.0%, although statistically significant, were short of the 5% change that investigators designing the trials saw as clinically significant.⁵ Of the five secondary outcomes, statistically significant improvements were not replicated in both trials (Table 1). Perhaps most relevant to treatment of CF, neither trial showed a statistical difference in the outcomes: quality of life or number of pulmonary exacerbations per year.

Clinical uncertainty

A survival benefit was not demonstrated in regulatory trials required by HC. Nevertheless, CFTR modulating therapies like LUM/IVA have generated considerable excitement because they build on emerging scientific knowledge of how CFTR mutations affect the functioning of mucus membrane cells. Another important and as yet unanswered question in the regulatory trials is whether LUM/IVA eliminates or modifies the exhaustive daily therapeutic programs undergone by CF patients.

Disease progression in CF patients is well understood⁶ with optimal current clinical therapy in persons with mild to moderate CF. FEV₁ as well as ppFEV₁ are valid disease progression markers although unreliable measures of symptoms.



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Disease progression, including mortality can be measured in clinical studies, but the trials need to be much longer than the 24 weeks required by the regulators. Randomized controlled trials of 3 years duration have been conducted for other therapeutic interventions in CF.⁷ A recent observational study offers some evidence to clinicians regarding LUM/IVA performance outside of a clinical trial. In a cohort of 116 patients followed for 11 months after initiating LUM/IVA treatment, 46 (39.7%) reported adverse effects related to LUM/IVA: 38 (32.7%) had pulmonary adverse effects and 20 (17.2%) discontinued treatment. Individuals with a ppFEV₁ of ≤ 40% had proportionally higher rates of adverse effects and discontinuation.⁸ This lower quality evidence demonstrates a higher rate of drug intolerance

than seen in the RCTs and suggests that people with more severe disease are more likely to discontinue the drug due to adverse effects.

Conclusions

- Lumacaftor/ivacaftor (Orkambi) is a new combination drug for the treatment of cystic fibrosis.
- Health Canada granted regulatory approval for this drug combination based on two 24-week placebo-controlled studies showing a 3% improvement with the drug in a lung function test (ppFEV₁).
- **There is insufficient evidence at the present time that lumacaftor/ivacaftor improves quality of life, morbidity or mortality in patients with cystic fibrosis.**

Table 1: LUM/IVA findings at recommended dose for people with homogeneous F508del CFTR mutations

Secondary efficacy outcomes reported at 24 weeks	Trial 1 ³ (n = 374)	Trial 2 ⁴ (n = 376)
Relative change in ppFEV ₁ - percent change relative to the baseline FEV ₁	NS	Statistically significant
Absolute change in body mass index (BMI) <i>a measure of nutritional status</i>	NS	Statistically significant
Absolute change in CFQ-R respiratory domain score <i>a measure of quality of life</i>	NS	NS
Response rate - relative change in % of patients with a ≥ 5% relative change in ppFEV ₁	NS	Statistically significant OR 2.4; 95% CI 1.5-3.7
Number of pulmonary exacerbation events per year	NS	NS

CFQ-R = Cystic Fibrosis Questionnaire – Revised

NS = not statistically significant

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