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Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: a systematic review and economic evaluation

Steven J Edwards,* Benjamin G Farrar, Kate Ennis, Nicole Downes, Victoria Wakefield, Isaac Mackenzie, Archie Walters and Tracey Jhita

BMJ-TAG, BMJ Group, London, UK

*Corresponding author sedwards@bmj.com

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Scientific summary

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis: a systematic review and economic evaluation

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Scientific summary

Background

Cystic fibrosis (CF) is a life-limiting genetic condition that is most often diagnosed through newborn screening. There are over 9000 people with CF in England, and 89% of these people have at least one *F508del* mutation on the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. CF affects organ systems throughout the body, including the digestive system and lungs. Most people with CF experience progressive lung function loss over their lifetime, and lung disease is the primary cause of death for people with CF.

Before the availability of CFTR modulator therapies, established clinical management (ECM) of CF involved treating the symptoms of CF, rather than the underlying cause of the disease. Existing therapies include inhaled mucolytics, bronchodilators, antibiotics and enzyme replacement therapy. A multidisciplinary team are involved in care for people with CF, which includes physiotherapists, psychologists, dietitians and social workers, in addition to specialist nurses and doctors.

Cystic fibrosis transmembrane conductance regulator gene modulator therapies treat the underlying cause of CF by altering the form or function of the CFTR protein. CFTR modulators have been available through the NHS via managed access agreements:

- Lumacaftor/ivacaftor (LUM/IVA) has been available for people aged ≥ 6 years with CF and two *F508del* copies (F/F genotype) since October 2019, and currently it is available for people aged ≥ 1 year with CF and an F/F genotype.
- Tezacaftor/ivacaftor (TEZ/IVA) has been available for people aged ≥ 12 years with CF and an F/F genotype or one *F508del* copy and an eligible residual function mutation (F/RF genotype) since October 2019, and currently it is available for people aged ≥ 6 years with CF and an F/F or F/RF genotype.
- Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been available for people aged ≥ 12 years with CF and a single *F508del* copy with another eligible mutation [F/F, F/RF, F/minimal function (F/MF) or F/Gating genotype] since August 2019 through compassionate access, and more widely since August 2020. Currently, ELX/TEZ/IVA is available for people aged ≥ 2 years with CF and an F/F, F/RF, F/MF or F/Gating genotype.

The clinical effectiveness and safety of CFTR modulator combination therapies has been studied in clinical trials, and through real-world data collection, notably through a data collection agreement between the National Institute for Health and Care Excellence (NICE), the UK Cystic Fibrosis Trust, Vertex Pharmaceuticals (Boston, MA, USA), NHS England and NHS Improvement.

Objectives

The objective of this research is to compare the clinical effectiveness and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA with each other and with ECM for treating CF in England for people with at least one *F508del* mutation.

Methods

A de novo systematic literature review (SLR) was conducted to identify relevant studies through searches of electronic databases [MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials)] up to February 2023, from bibliographies of retrieved studies including a relevant Cochrane review, clinical trial registers, relevant conferences and from an evidence submission provided by Vertex Pharmaceuticals. Pre-specified eligibility criteria were used to identify studies to be included in the SLR. Two independent reviewers appraised the titles and abstracts of identified records and performed an evaluation of full texts, with a third reviewer used to resolve discrepancies. Data from included studies were extracted by one reviewer and validated by a second. Study quality was assessed by a single reviewer

at both the study and outcome level using standard checklists, and was then validated by a second reviewer. Where sufficient data were available for an outcome measure within a genotype and age-group of interest, Bayesian network meta-analyses (NMAs) were performed using Markov chain Monte Carlo simulations. The key outcomes of the clinical effectiveness review were changes in per cent predicted forced expiratory volume in 1 second ($ppFEV_1$); changes in weight-for-age *z*-score; and the frequency of pulmonary exacerbations requiring intravenous (IV) antibiotics. Additional real-world evidence was obtained through targeted searches of electronic databases, a data request to the UK CF Registry and an appraisal of the final report of the data collection agreement produced by Vertex Pharmaceuticals.

A de novo economic model was developed to assess the cost-effectiveness of the three CFTR modulator treatments, using an individual patient simulation model. The economic model uses a Cox proportional hazards (CPH) model developed by Liou *et al*. (Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;**153**:345–52) to predict patient survival based on changes in individual characteristics over a patient's lifetime. Individual baseline characteristics are sourced from either patient-level trial data, assumptions or population data from the UK CF Registry. The populations modelled are in line with the expected marketing authorisation of each intervention. Therefore, any patients who start the model in each treatment arm before the marketing authorisation age is reached for that specific CFTR modulator receives ECM only.

Estimates of treatment effectiveness, based on change in $ppFEV_1$, weight-for-age *z*-score and rate of pulmonary exacerbations, were taken from the clinical assessment of the evidence. Due to a lack of long-term data available on the treatment effectiveness of CFTR modulators over a patient's lifetime, a number of assumptions needed to be made, based on clinical expert opinion and published evidence.

Utilities based on $ppFEV_1$ severity (< 40, 40–69, ≥ 70) were obtained from the key trial of LUM/IVA; this was the only CFTR modulator trial that collected EuroQol-5 Dimensions (EQ-5D) data. Costs were obtained from standard UK sources, with the costs of CFTR modulator treatments provided by the company, including confidential commercial discounts.

The economic model used a lifetime horizon (up to a maximum of 100 years), and the analysis is from an NHS perspective. Costs and quality-adjusted life-years (QALYs) have been discounted at 3.5%, as per the NICE reference case. The impact of uncertainty in key assumptions and model parameters was tested through a range of scenario analyses and probabilistic sensitivity analysis.

Results

Nineteen relevant studies and seven associated open-label extension studies were included for data extraction from the SLR. Sixteen of these were Phase III (n = 14), Phase II (n = 1) or Phase IV (n = 1) randomised controlled trials, most of which were assessed to be high quality. Three non-randomised Phase III trials of children with CF were also included. The clinical trials were international studies but were assessed to have good generalisability to clinical practice in England.

Across genotypes, treatment with ELX/TEZ/IVA led to large and statistically significant acute increases in $ppFEV_1$, weight-for-age *z*-score and pulmonary exacerbations requiring IV antibiotics compared with ECM, and LUM/IVA and TEZ/IVA where available. Clinical experts advised the External Assessment Group (EAG) that the magnitude of these effects with ELX/TEZ/IVA is clinically meaningful and likely to lead to increased survival relative to ECM. LUM/IVA and TEZ/IVA were also associated with acute increases in $ppFEV_1$, and reductions in pulmonary exacerbations requiring IV antibiotics compared with ECM. LUM/IVA was associated with an increase in weight-for-age *z*-score relative to ECM. The effect sizes for LUM/IVA and TEZ/IVA were smaller than for ELX/TEZ/IVA. Nevertheless, the effects are still expected to be clinically meaningful and be associated with better long-term lung function and increased survival than ECM.

The main outstanding clinical uncertainty is the long-term effect of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the annual rate of $ppFEV_1$ decline for people with CF. No head-to-head comparative effectiveness data are available for these

long-term outcomes, and where uncontrolled long-term data are available, follow-up was often limited to 2–3 years. Real-world data collection as part of the data collection agreement did not result in robust long-term data for LUM/IVA or TEZ/IVA because of the rapid transition of most patients to ELX/TEZ/IVA once it became available. For ELX/TEZ/IVA, the unforeseen COVID-19 pandemic likely had a strong confounding effect on clinical trial data and real-world evidence collected during periods of viral shielding. The EAG considers the magnitude of any effects of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA on the long-term annual rate of $ppFEV_1$ decline for people with CF to be highly uncertain, but considers there to be:

- little evidence to suggest that LUM/IVA meaningfully reduces the long-term rate of $ppFEV_1$ decline compared with ECM (EAG preferred assumption: 0% reduction in rate of $ppFEV_1$ decline compared with ECM)
- some evidence that TEZ/IVA reduces the long-term rate of $ppFEV_1$ decline compared with ECM, with a small effect size (EAG preferred assumption: 17.18% reduction in rate of $ppFEV_1$ decline compared with ECM)
- good evidence that ELX/TEZ/IVA reduces the long-term rate of $ppFEV_1$ decline compared with ECM, with a highly uncertain magnitude (EAG preferred assumption: 61.00% reduction in rate of $ppFEV_1$ decline compared with ECM).

Additional uncertainty was noted concerning:

- the effects of CFTR modulator therapy on EQ-5D measurements of health-related quality of life in CF
- the effects of CFTR modulator therapy on the long-term rate of pulmonary exacerbations, which were inconsistently reported across clinical trials
- clinically important differences for acute changes in $ppFEV_1$ and weight-for-age *z*-score
- the rate of co-adherence to non-CFTR modulator therapies and the effects of reduced co-adherence on CFTR modulator effectiveness
- the long-term adverse event (AE) profile of CFTR modulators, specifically regarding mental health outcomes, hypertension and cataracts and lens opacities.

The NICE typically considers interventions a cost-effective use of the NHS resources if the incremental cost-effectiveness ratio (ICER) sits below a cost-per-QALY threshold of £20,000–30,000. None of the EAG's base-case ICERs (either pairwise vs. ECM alone or full incremental results, used when more than two alternative treatments are available) were lower than £30,000, and were substantially higher than this upper threshold. For the F/F population, all three modulator treatments have marketing authorisation. The ICERs from the full incremental analysis within the population showed that both LUM/IVA and TEZ/IVA were extendedly dominated in the F/F population (i.e. the ICERs were higher than a more effective treatment, ELX/TEZ/IVA). In the F/RF population, TEZ/IVA was also extendedly dominated by ELX/TEZ/IVA.

In the F/MF and F/Gating population, only ELX/TEZ/IVA is available. Base-case deterministic results were similar across the two populations when compared with ECM.

The EAG ran a range of scenario analyses to explore the impact of different assumptions. The key drivers of cost-effectiveness for all genotype populations were the long-term assumptions of the treatment effect of CFTR modulators on $ppFEV_1$ decline. None of the implemented scenarios resulted in an ICER below £30,000 and were substantially higher than this upper threshold.

The EAG also implemented an additional exploratory scenario to investigate the impact of ELX/TEZ/IVA preventing any long-term lung decline post treatment initiation. This exploratory scenario also assumes that the direct treatment effect of ELX/TEZ/IVA on the rate of pulmonary exacerbations lasts for a lifetime. Although this scenario resulted in lower ICERs for ELX/TEZ/IVA than the base case, they were still not below the £30,000 threshold, despite a severity modifier of 1.2 being applied, a 1.5% discount rate and highly optimistic assumptions regarding the long-term effectiveness of ELX/TEZ/IVA.

Conclusions

Elexacaftor/tezacaftor/ivacaftor is associated with large and clinically meaningful acute improvements in lung function and weight-for-age *z*-score in people with CF, and results in a reduction in the frequency of pulmonary exacerbations. In the long term, ELX/TEZ/IVA reduces the rate of ppFEV$_1$ decline, although the magnitude of this reduction is uncertain. TEZ/IVA and LUM/IVA are also associated with improved clinical outcomes for people with CF relative to ECM, but with a smaller benefit than ELX/TEZ/IVA.

Despite the improved clinical outcomes observed, none of the included CFTR modulators would be considered cost-effective based on the NICE threshold of £20,000–30,000 per QALY gained. This is largely driven by the high acquisition costs of CFTR modulator treatments.

If multiple treatments are made available in clinical practice, it is unknown if patients may switch between CFTR modulators once they reach the age at which a more effective treatment holds marketing authorisation (i.e. TEZ/IVA or ELX/TEZ/IVA). In addition, if more than one CFTR modulator was available in routine clinical practice, patients may be started on another on discontinuation. There is currently a lack of both clinical effectiveness and cost-effectiveness data on sequences of CFTR modulator treatments.

The following areas for future research are recommended:

- further data collection concerning the long-term effects of CFTR modulators on the rate of ppFEV$_1$ decline, frequency of pulmonary exacerbations and changes in infection status in people with CF
- the impact of co-adherence to ECM medications for people treated with CFTR modulators, and the effects of discontinuing CFTR modulators
- the lifetime AE profile of CFTR modulators, including regarding liver disease, cataracts, lens opacities, hypertension and adverse effects on a person's mental health
- further validation of the CPH model used to model the impact of changes in patient characteristics over time on survival in the UK population.

Study registration

This study is registered as PROSPERO CRD42023399583.

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This article

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