BMJ TAG

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CO101

Estimating the long-term impact of cystic fibrosis transmembrane conductance regulator (CFTR) modulator treatments on the annual decline of per cent predicted forced expiratory volume in one second ($ppFEV_1$) compared to established clinical management (ECM)

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Introduction

- Cystic fibrosis (CF) is a life-limiting disease, characterised by progressive loss of lung function and severe respiratory infections.
- CFTR modulators are the first treatments to address the underlying cause of CF.
- In a NICE multiple technology appraisal (TA998), the external assessment group (EAG) assessed the clinical and cost-effectiveness of three CFTR modulator treatments: elexacafor/tezacaftor/ivacaftor (ELX/TEZ/IVA), tezacaftor/ivacaftor (TEZ/IVA), and lumacaftor/ivacaftor (LUM/IVA) versus ECM.
- Few long-term or head-to-head data are available comparing the long-term impact of the annual rate of $ppFEV_1$ decline compared to ECM. Alternative approaches used fail to exclude adequate data on the acute effects of treatment, which may overestimate the long-term effectiveness.

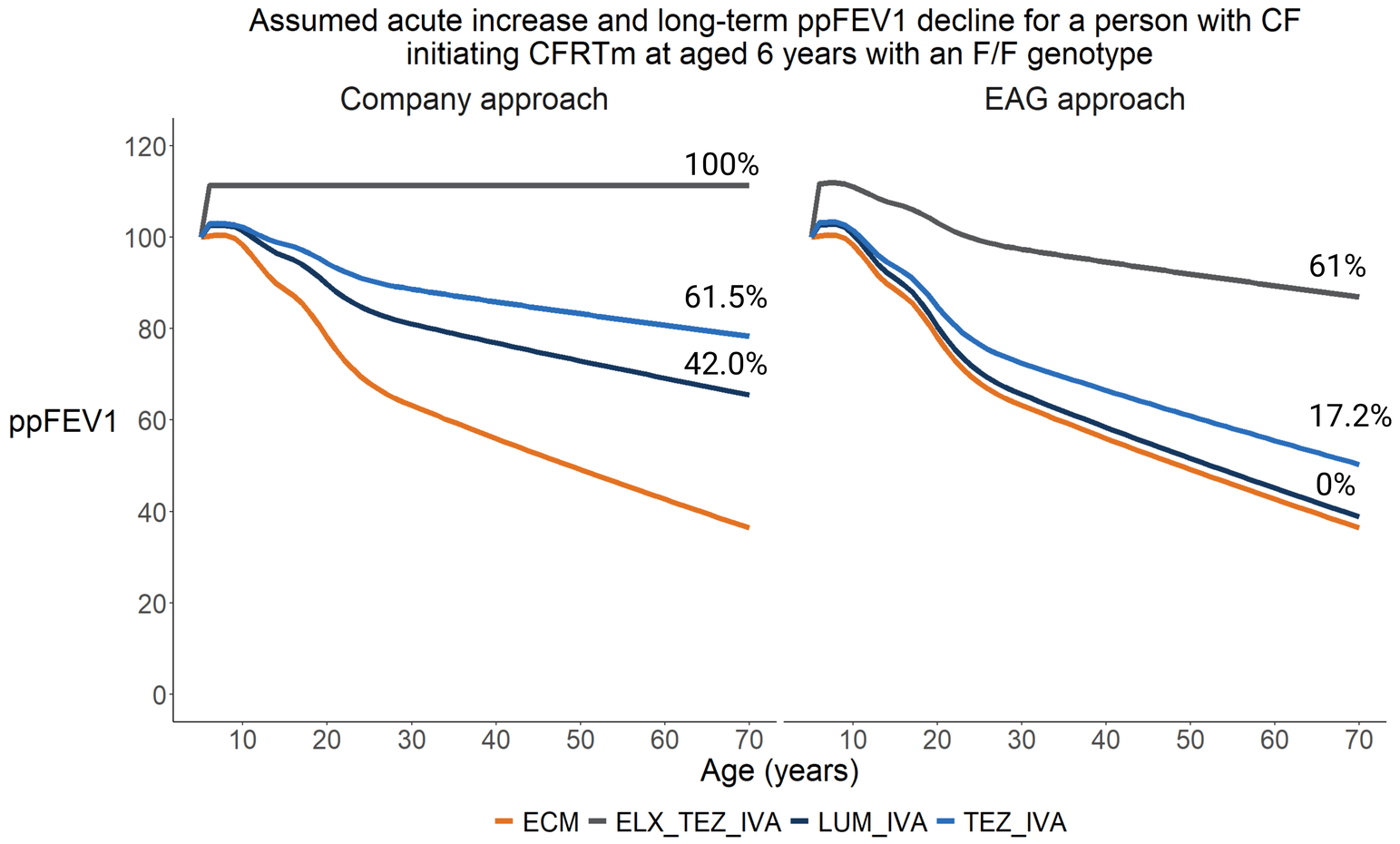
Objective

Estimate the long-term annual decline of $ppFEV_1$ in patients receiving CFTR modulator treatments, considering a lack of robust long-term comparative data and potential COVID-19 pandemic confounding effects on existing single-arm trial data.

Methods

- Identified two studies using UK CF registry data of people treated with IVA between 2008 and 2016[1, 2] Using data reported on the causal treatment effect of IVA on the long-term rate of $ppFEV_1$ decline, a relative reduction in $ppFEV_1$ decline was estimated for people treated with IVA compared to ECM (38%, 95% CI: -12% to 87%).
  - *ELX/TEZ/IVA and TEZ/IVA relative reduction* = Adjusted known rate of decline of IVA monotherapy based on the ratio of the acute effects in observed data from short-term clinical trials.
  - *LUM/IVA relative reduction* = No robust evidence from the pivotal randomised controlled trial (RCT) or systematic literature review of a reduction in the rate of decline of $ppFEV_1$ for LUM/IVA compared to ECM.

Results



N.B. Due to data confidentiality, the same acute increase in response to treatment with CFTR modulators is applied to both the company and the EAG approach. The relative rates of decline shown represent those applied after the first NICE technology appraisal committee meeting, and before the submission of additional confidential data from the company for ELZ/TEZ/IVA.

Abbreviations: CF, cystic fibrosis; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; EAG, external assessment group; ECM, established clinical management; ELX_TEZ_IVA, elexacafor/tezacaftor/ivacaftor; LUM_IVA, lumacaftor/ivacaftor, TEZ_IVA, tezacaftor/ivacaftor; $ppFEV_1$, per cent predicted forced expiratory volume in one second

Conclusions

- Longer-term data since published are consistent with a larger relative reduction in $ppFEV_1$ decline for ELX/TEZ/IVA,[3] but are uncontrolled and follow-up is still limited to <4 years.
- Future modelling may prefer to use the directly observed rate and shape of $ppFEV_1$, or as a calibration, as longer follow-up data emerges.

References

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3. Daines CL, Polineni D, Tullis E, Costa S, Linnemann RW, Mall MA, *et al.* Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Adults and Adolescents with Cystic Fibrosis and at Least One F508del Allele: A Phase 3 Open-Label Extension Study. *American Journal of Respiratory and Critical Care Medicine* 2025; **211**: 1901-14.

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