Cochrane Database of Systematic Reviews - - Cochrane Review

CFTR modulator monotherapy for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del)

Code: CD016290 **Year:** 2026 **Date:** 2026 - updated 27 June 2025 **Author:** Matthew Heneghan

Study design (if review, criteria of inclusion for studies)

Parallelâ€•group randomised controlled trials (RCTs) comparing any single CFTR modulator to placebo or any other single CFTR modulator

Participants

Patients with CF of any age or disease severity with class II variants. The class II CFTR gene variant, F508del, is the commonest CFâ€•causing variant found in up to 90% of people with CF. The F508del variant lacks meaningful CFTR function: the faulty protein is degraded before reaching the cell membrane, where it would normally transport salt across the epithelial membrane.

Interventions

Corrective therapy with CFTR modulators. This review evaluates treatment with single modulators (monotherapy).

Outcome measures

Critical outcomes: survival, quality of life (total score and respiratory domain), and FEV1 % predicted, relative and absolute change from baseline. Important outcomes: adverse effects and time to first pulmonary exacerbation. Authors planned to assess outcomes in the immediate term, short term, and longer term.

Main results

10 earlyâ€•phase placeboâ€•controlled RCTs (424 participants) assessing eight different drugs (4PBA, CPX, N6022, cavosonstat, lumacaftor, FDL169, GLPG2222, and riociguat) in adults; one 4PBA study additionally included adolescents (age â‰¥ 14 years). The longest study lasted just 29 days, so authors could only assess immediateâ€•term outcomes. Only two studies received no funding from pharmaceutical companies. The main results are for lumacaftor and cavosonstat, which were the only drugs selected for further investigation in subsequent studies. Investigators reported no deaths, but also no clinically relevant improvements in quality of life. There was insufficient evidence to determine effects on any measure of lung function. No studies demonstrated differences in the risk of mild, moderate, or severe adverse effects, including pulmonary exacerbations, between CFTR modulator monotherapy and placebo. The clinical relevance of adverse effects is difficult to assess, because each occurred in only a few participants per trial. , rating The certainty of the evidence (assessed for two comparisons, lumacaftor versus placebo and cavosonstat versus placebo): very low.

Authors' conclusions

There is a lack of evidence to support monotherapy with a CFTR modulator for pwCF who have two F508del variants (F508del/F508del).

https://doi.org//10.1002/14651858.CD016290

See also

Heneghan M, Smith S, Jahnke N, Nevitt S, Southern KW. CFTR modulator monotherapy for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database of Systematic Reviews 2026, Issue 5. Art. No.: CD016290. DOI: 10.1002/14651858.CD016290. Accessed 29 June 2026.

Keywords

Child; Adult; Adolescent; Aminophenols; CFTR Modulators; Genetic Predisposition to Disease; pharmacological_intervention; VX-770; ivacaftor;