Study: Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele
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Published: New England Journal of Medicine Oct. 2019. N Engl J Med 2019;381:1809-19.

This study is a phase three, randomized, double-blind, trial of elexacaftor-tezacaftor-ivacaftor versus placebo over 24 weeks in cystic fibrosis (CF). 403 participants over 12 years old with one Phe508del mutation and one minimal function mutation of the CF transmembrane conductance regulator (CFTR) were recruited. The primary endpoint was change from baseline percentage forced expiratory volume in one second (FEV1) at week 4. The intervention arm had a 13.8 % higher FEV1 at 4 weeks ($p<0.001$). Improvements in FEV1 were sustained to week 24 (14.3%). Further significant findings included reduced exacerbation rate, increased BMI, increased quality of life scores and reduced sweat chloride. A favourable safety profile was demonstrated.

Following an encouraging Phase 2 trial, this study investigated adding a further CFTR corrector, elexacaftor, to tezacaftor-ivacaftor.[1] Trial design including stratification by FEV1 severity, gender and age. Significant benefits were displayed in a population in which previous CFTR modulator therapies were ineffective. FEV1 improvement with this therapy exceeded the previous CFTR modulator benchmark of ivacaftor in Gly551Asp mutations.[2] FEV1 change is an appropriate endpoint, correlating well with clinical status in CF, while pulmonary exacerbations are associated with disease progression. Participants whose baseline FEV1 decreased below 40% prior to trial commencement were not excluded if initial screening FEV1 criteria was 40-90% predicted. The FEV1 change seen in these participants was similar to overall results, which is promising for those with severe respiratory disease.

CF therapies were ineffective in those heterozygous for Phe508del with a second 'minimal function' CFTR mutation, defined by lack of responsiveness to current modulator therapies. Following approval in the United States in October 2019 as *Trikafta*, the European Medicines Agency approved *Kaftrio* in August 2020.[3][4] Approximately 90% of the worlds CF population can now be treated. Elexacaftor-tezacaftor-ivacaftor is also approved for those homozygous for the Phe508del mutation, having shown superiority to existing tezacaftor-ivacaftor therapy in a recent RCT.[5] Guidelines are under development, with therapy commencement planned in all eligible candidates in Ireland in late 2020. Future challenges include targeting restoration of CFTR function in all CF genotypes, especially mutations for which current modulators show no benefit. In particular, extension of current treatments to younger age groups is vital to allow early introduction of disease modifying therapies.

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[4] European Medicines Agency. *Kaftrio (ivacaftor / tezacaftor / elexacaftor) An overview of Kaftrio and why it is authorised in the EU. https://www.ema.europa.eu/en/documents/overview/kaftrio-epar-medicine-overview_en.pdf (accessed 29 August 2020).*
[5] Heijerman HGM, McKone EF et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet* 2019; 394(10212): 1886-1888.