primary studies - published RCT

Safety and efficacy of vanzacaftor-tezacaftor-deutivacaftor in adults with cystic fibrosis: randomised, double-blind, controlled, phase 2 trials.

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

Two phase 2 clinical trials: 1) A phase 2 randomised, double-blind, active-controlled study 2) A phase 2 randomised, double-blind, controlled, proof-of-concept study. These clinical trials are registered with ClinicalTrials.gov, NCT03911713 and NCT03912233

Participants

Patients with cystic fibrosis who were aged 18 years or older. Trial 1) participants with CFTR gating mutations. Trial 2) participants with cystic fibrosis and heterozygous for F508del and a minimal function mutation (F/MF genotypes) or homozygous for F508del (F/F genotype).

Interventions

Trial 1) Participants were randomly assigned to receive either ivacaftor 150 mg every 12 h, deutivacaftor 25 mg once daily, deutivacaftor 50 mg once daily, deutivacaftor 150 mg once daily, or deutivacaftor 250 mg once daily in a 1:1:2:2:2 ratio. Trial 2) Participants with F/MF genotypes were randomly assigned 1:2:2:1 to receive either 5 mg, 10 mg, or 20 mg of vanzacaftor in combination with tezacaftor-deutivacaftor or a triple placebo for 4 weeks, and participants with the F/F genotype were randomly assigned 2:1 to receive either vanzacaftor (20 mg)-tezacaftor-deutivacaftor or tezacaftor-ivacaftor active control for 4 weeks, following a 4-week tezacaftor-ivacaftor run-in period.

Outcome measures

Trial 1) The primary endpoint was absolute change in ppFEV(1) from baseline at week 12. Trial 2) Primary endpoints for part 1 and part 2 were safety and tolerability and absolute change in ppFEV(1) from baseline to day 29. Secondary efficacy endpoints were absolute change from baseline at day 29 in sweat chloride concentrations and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score.

Main results

In study VX18-561-101, participants treated with deutivacaftor 150 mg once daily (n=23) or deutivacaftor 250 mg once daily (n=24) had mean absolute changes in ppFEV(1) of 3·1 percentage points (95% CI -0·8 to 7·0) and 2·7 percentage points (-1·0 to 6·5) from baseline at week 12, respectively, versus -0·8 percentage points (-6·2 to 4·7) with ivacaftor 150 mg every 12 h (n=11); the deutivacaftor safety profile was consistent with the established safety profile of ivacaftor 150 mg every 12 h. In study VX18-121-101, participants with F/MF genotypes treated with vanzacaftor (5 mg)-tezacaftor-deutivacaftor (n=9), vanzacaftor (10 mg)-tezacaftor-deutivacaftor (n=19), vanzacaftor (20 mg)-tezacaftor-deutivacaftor (n=20), and placebo (n=10) had mean changes relative to baseline at day 29 in ppFEV(1) of 4·6 percentage points (-1·3 to 10·6), 14·2 percentage points (10·0 to 18·4), 9·8 percentage points (5·7 to 13·8), and 1·9 percentage points (-4·1 to 8·0), respectively, in sweat chloride concentration of -42·8 mmol/L (-51·7 to -34·0), -45·8 mmol/L (95% CI -51·9 to -39·7), -49·5 mmol/L (-55·9 to -43·1), and 2·3 mmol/L (-7·0 to 11·6), respectively, and in CFQ-R respiratory domain score of 17·6 points (3·5 to 31·6), 21·2 points (11·9 to 30·6), 29·8 points (21·0 to 38·7), and 3·3 points (-10·1 to 16·6), respectively. Participants with the F/F genotype treated with vanzacaftor (20 mg)-tezacaftor-deutivacaftor (n=18) and tezacaftor-ivacaftor (n=10) had mean changes relative to baseline (taking tezacaftor-ivacaftor) at day 29 in ppFEV(1) of 15·9 percentage points (11·3 to 20·6) and -0·1 percentage points (-6·4 to 6·1), respectively, in sweat chloride concentration of -45·5 mmol/L (-49·7 to -41·3) and -2·6 mmol/L (-8·2 to 3·1), respectively, and in CFQ-R respiratory domain score of 19·4 points (95% CI 10·5 to 28·3) and -5·0 points (-16·9 to 7·0), respectively. The most common adverse events overall were cough, increased sputum, and headache. One participant in the vanzacaftor-tezacaftor-deutivacaftor group had a serious adverse event of infective pulmonary exacerbation and another participant had a serious rash event that led to treatment discontinuation. For most participants, adverse events were mild or moderate in severity.

Authors' conclusions

Once-daily dosing with vanzacaftor-tezacaftor-deutivacaftor was safe and well tolerated and improved lung function, respiratory symptoms, and CFTR function. These results support the continued investigation of vanzacaftor-tezacaftor-deutivacaftor in phase 3 clinical trials compared with elexacaftor-tezacaftor-ivacaftor.

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See also

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Keywords

CFTR Modulators; Genetic Predisposition to Disease; pharmacological_intervention; placebo; VX-770; VX-121; ivacaftor; Aminophenols; tezacaftor; VX-661; vanzacaftor;