primary studies - published RCT

Vanzacaftor-tezacaftor-deutivacaftor versus elexacaftor-tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials.

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

Two randomised, active-controlled, double-blind, phase 3 trials

Participants

Individuals aged 12 years and older with stable cystic fibrosis with F508del-minimal function (SKYLINE Trial VX20-121-102) or with F508del-F508del, F508del-residual function, F508del-gating, or elexacaftor-tezacaftor-ivacaftor-responsive-non-F508del genotypes (SKYLINE Trial VX20-121-103) were enrolled at 126 and 159 international sites, respectively.

Interventions

Vanzacaftor-tezacaftor-deutivacaftor compared with standard of care elexacaftor-tezacaftor-ivacaftor. Patients were enrolled at 126 and 159 international sites, respectively. Eligible individuals were entered into a 4-week run-in period, during which they received elexacaftor (200 mg once daily), tezacaftor (100 mg once daily), and ivacaftor (150 mg once every 12 h) as two fixed-dose combination tablets in the morning and one ivacaftor tablet in the evening. They were then randomly assigned (1:1) to either elexacaftor (200 mg once daily), tezacaftor (100 mg once daily), and ivacaftor (150 mg once every 12 h) as two fixed-dose combination tablets in the morning and one ivacaftor tablet in the evening, or vanzacaftor (20 mg once daily), tezacaftor (100 mg once daily), and deutivacaftor (250 mg once daily) as two fixed-dose combination tablets in the morning, for the 52-week treatment period. All participants received matching placebo tablets to maintain the treatment blinding.

Outcome measures

The primary endpoint for both trials was absolute change in FEV(1) % predicted from baseline (most recent value before treatment on day 1) through week 24 (with non-inferiority of vanzacaftor-tezacaftor-deutivacaftor shown if the lower bound of the 95% CI for the primary endpoint was -3·0 or higher). Efficacy was assessed in all participants with the intended CFTR genotype who were randomly assigned to treatment and received at least one dose of study treatment during the treatment period. Safety was assessed in all participants who received at least one dose of study drug during the treatment period.

Main results

In Trial VX20-121-102 between Sept 14, 2021, and Oct 18, 2022, 488 individuals were screened, of whom 435 entered the 4-week run-in period, and subsequently 398 were randomly assigned and received at least one dose of elexacaftor-tezacaftor-ivacaftor (n=202) or vanzacaftor-tezacaftor-deutivacaftor (n=196). Median age was 31·0 years (IQR 22·6-38·5), 163 (41%) of 398 participants were female, 235 (59%) were male, and 388 (97%) were White. In Trial VX20-121-103, between Oct 27, 2021, and Oct 26, 2022, 699 individuals were screened, of whom 597 entered the 4-week run-in period, and subsequently 573 participants were randomly assigned and received at least one dose of elexacaftor-tezacaftor-ivacaftor (n=289) or vanzacaftor-tezacaftor-deutivacaftor (n=284). Median age was 33·1 years (IQR 24·5-42·2), 280 (49%) of 573 participants were female, 293 (51%) were male, and 532 (93%) were White. The absolute change in least squares mean FEV(1) % predicted from baseline through week 24 for Trial VX20-121-102 was 0·5 (SE 0·3) percentage points in the vanzacaftor-tezacaftor-deutivacaftor group versus 0·3 (0·3) percentage points in the elexacaftor-tezacaftor-ivacaftor group (least squares mean treatment difference of 0·2 percentage points [95% CI -0·7 to 1·1]; p

Authors' conclusions

Vanzacaftor-tezacaftor-deutivacaftor is non-inferior to elexacaftor-tezacaftor-ivacaftor in terms of FEV(1) % predicted, and is safe and well tolerated. Once daily dosing with vanzacaftor-tezacaftor-deutivacaftor reduces treatment burden, potentially improving adherence, compared with the twice daily regimen of the current standard of care. The restoration of CFTR function and the potential variants

treated are also considerations that should be compared with currently available CFTR modulators.

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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; deutivacaftor; elexacaftor; VX-445; VX-561; Trikafta;