



ERS CONGRESS | 2026

5-9 September | Barcelona, Spain

RCT Abstract - Safety and efficacy of vanzacaftor/tezacaftor/deutivacaftor in children with cystic fibrosis aged 2 to 5 years (TIMBERLINE Trial VX21-121-105): a phase 3, open-label study

M. Mall (Berlin, Germany), J. Rayment (Vancouver, Canada), G. Davies (London, United Kingdom), J. Gaffin (Boston, United States), J. Hoppe (Colorado, United States), A. Kasi (Atlanta, United States), E. McKone (Dublin, Ireland), B. Ramsey (Seattle, United States), J. Taylor (Denver, United States), E. Tullis (Toronto, Canada), E. McDougall (Boston, United States), R. Pottackal (Boston, United States), R. Zahigian (Boston, United States), K. Krone (Boston, United States), M. Jennings (Boston, United States), J. Chmiel (Indianapolis, United States)

Background Vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) was efficacious and safe in people with cystic fibrosis (CF) aged ≥ 6 years, providing further restoration of CFTR function compared to elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). We assessed VNZ/TEZ/D-IVA safety and efficacy in children aged 2-5 years.

Methods This phase 3, 24-week, open-label study enrolled children with CF aged 2-5 years with an ELX/TEZ/IVA-responsive genotype. Primary endpoint was safety and tolerability. Secondary endpoints included absolute change in sweat chloride and proportion of children with sweat chloride < 60 mmol/L and < 30 mmol/L. Prior to the 24-week VNZ/TEZ/D-IVA treatment period, all children were either on a stable regimen of ELX/TEZ/IVA for ≥ 28 days before screening or had a 4-week ELX/TEZ/IVA run-in.

Findings 67 children received ≥ 1 dose of VNZ/TEZ/D-IVA, all of whom completed the study. Mean exposure was 24.0 weeks (SD, 0.5). Sixty-four children (95.5%) had adverse events (AE), predominantly mild (52.2%) or moderate (38.8%) in severity. Two children (3.0%) had serious AEs; neither were considered related to VNZ/TEZ/D-IVA. No children discontinued due to AEs. From the ELX/TEZ/IVA baseline, mean sweat chloride decreased by 9.6 mmol/L (95% CI: -12.1 to -7.0) to a mean of 28.9 mmol/L by week 24, with 92.4% of children achieving levels below the diagnostic threshold for CF (< 60 mmol/L) and 65.2% of children reaching levels < 30 mmol/L.

Interpretation VNZ/TEZ/D-IVA was generally safe and well-tolerated. Sweat chloride decreased, with 65.2% of children reaching levels < 30 mmol/L, indicating additional CFTR function improvement beyond ELX/TEZ/IVA. These results show the safety and potential for greater restoration of CFTR function with VNZ/TEZ/D-IVA in preschool children with CF.