

(vs $2.1 \pm 2.0 \mu\text{A}/\text{cm}^2$ for vehicle, $p < 0.001$, representing 48% restoration of wild-type CFTR I_{sc}). CFTR inhibition with CFTR Inh-172 mirrored these responses. Monolayers demonstrated improved ASL ($11.9 \pm 4.9 \mu\text{m}$ ELX/TEZ/IVA vs $5.3 \pm 2.5 \mu\text{m}$ vehicle control, $p < 0.05$, 56% improvement with ELX/TEZ/IVA vs vehicle normalized to baseline measurements); acquisition of MCT and CBF data was limited because of variable degrees of differentiation. On an individual basis, ELX/TEZ/IVA-treated Fsk-stimulated I_{sc} correlated with augmented ASL with ELX/TEZ/IVA treatment ($r = 0.74$, $p < 0.001$). ELX/TEZ/IVA-treated I_{sc} also moderately correlated with 6-month post-ELX/TEZ/IVA sweat chloride ($r = 0.59$, $p < 0.05$) but was not related to absolute change in FEV_{1pp} ($r = 0.26$, $p > 0.05$) in this preliminary analysis. Increases in ASL correlated with improvements in FEV_{1pp} after 6 months of treatment ($r = 0.58$, $p < 0.05$) Stratification based on prior modulator status is in progress.

Conclusions: Results from the PROMISE HNE substudy demonstrate that HNECs derived from participants in a multicenter study reproduced improvements in CFTR activity and ASL depth, including the treatment effects of ELX/TEZ/IVA CFTR modulator treatment. At interim analysis, changes in I_{sc} correlated with sweat chloride, and ASL depth correlated with clinical response (FEV_{1pp}), consistent with relationships established in ivacaftor-treated HNECs in the GOAL study. These findings provide additional confidence that HNECs are an important in vitro biomarker of treatment response to CFTR-directed therapies, including individual-level responses.

Acknowledgements: On behalf of the PROMISE Investigators. Supported by the Cystic Fibrosis Foundation and National Institutes of Health.

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Longitudinal improvements in clinical and functional outcomes following initiation of elxacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis

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Background: The advent of highly effective modulator therapies (HEMTs), including elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), for treatment of cystic fibrosis (CF) has resulted in remarkable clinical improvement for modulator-naïve patients and for those who have been treated with prior modulator therapies. Intranasal micro-optical coherence tomography (μOCT) has detected functional abnormalities in the mucociliary apparatus of people with CF. The objective was to characterize the effects of ELX/TEZ/IVA on nasal mucociliary clearance by μOCT and monitor the clinical changes conferred as a way to understand the effects.

Methods: Of 26 individuals aged 12 and older with at least one F508del mutation recruited, 24 were enrolled and followed over three visits: baseline and 1 (visit 2) and 6 months (visit 4) after initiation of ELX/TEZ/IVA therapy; the COVID-19 pandemic affected visit windows. Intranasal μOCT imaging was conducted at baseline and visit 2 as previously described; additional imaging for 18 months (visit 5) is in progress. Clinical outcomes, including percentage predicted forced expiratory volume in 1 second (FEV_{1pp}) and sweat chloride levels were computed as part of the parent Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function (PROMISE study). A blinded investigator team analyzed in vivo μOCT parameters including mucociliary transport (MCT) rate, ciliary beat frequency (CBF), and periciliary liquid depth (PCL) after

devising an improved stabilization algorithm. Analysis of airway surface liquid (ASL) depths was excluded because of the limited number of cases in which the necessary condition for measurement, which is preservation of a clear air layer between the mucus layer and the probe, was satisfied.

Results: Twenty-three subjects completed visits 1 and 2, and 18 completed visits 1, 2, and 4. Average age at baseline was 27 ± 8.7 , 69% were female, and 43% were on prior two-drug modulator therapy. No significant change in body mass index was found between the visits. FEV_{1pp} increased significantly (10.9%, 95% CI, 76.1–98.4%) by visit 2 and persisted at visit 4 (10.6%, 95% CI, 87.7–107.0; $p < 0.001$). Sweat chloride levels decreased significantly at visit 2 (-36.6 mmol/L , 95% CI, 40.9–54.9 mmol/L) and visit 4 (-41.3 mmol/L , 95% CI, 34.9–51.8 mmol/L) at visit 4 ($p < 0.001$). Analysis of μOCT images revealed significant improvement in MCT rate ($2.8 \pm 1.5 \text{ mm/min}$ at baseline vs $4.0 \pm 1.5 \text{ mm/min}$ at visit 2, $p = 0.048$), although no discernable changes were noted in CBF or PCL. When stratified based on use of prior modulator therapy, no significant differences were found for any μOCT metric. No significant correlations between change in MCT rates and change in FEV_{1pp} or sweat chloride from baseline to visit 2 were found.

Conclusions: Treatment with ELX/TEZ/IVA in people with CF, including those that were treatment naïve and those on prior modulator therapy, resulted in significant, sustained improvement in lung function and decreases in sweat chloride levels at ~10 months, consistent with recently published reports. Functional improvements in MCT rate were evident after initiation of ELX/TEZ/IVA therapy, which may partially explain the findings of better whole-lung mucus clearance and reduction in chronic infections reported previously. μOCT imaging in people with CF is sensitive to the treatment effect of HEMT and suggests better mucociliary transport as a mechanism of action underlying the clinical benefits for lung health.

Acknowledgements: On behalf of the PROMISE investigators.

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Multicenter validation of the CF-ABLE score as a predictor of outcome and therapeutic response in cystic fibrosis

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Background: The CF-ABLE (age, body mass index (BMI), lung function, number of exacerbations in the last 3 months) score is an easy-to-use prognostic scoring system that has been validated in a large cohort from the national Cystic Fibrosis Registry of Ireland. This weighted score ranges from 0 to 7 and predicts risk of poor outcome, defined as death or requirement for lung transplantation, over time using commonly available clinical parameters such as age, BMI, forced expiratory volume in 1 second (FEV₁), and exacerbation frequency. In the original study describing the score, people with CF (PwCF) with a score of 5 or greater were deemed to have a 26% risk of poor outcome within 4 years. The present study aimed to evaluate real-world clinical performance of the CF-ABLE score as a clinical predictor in CF. Because clinical endpoints such as mortality and transplantation are typically difficult to meet in time-limited clinical trials, we also investigated the effect of double- and triple-combination CFTR modulator therapy on CF-ABLE score.

Methods: PwCF (n = 611) were recruited from three large specialist CF centers in the United States and Ireland. Participants were enrolled between 2013 and 2015 and followed clinically for 4 years from the point of enrollment unless they transitioned to a CF-ABLE score of 5 or greater within 2 years, in which case the 4-year follow-up period commenced at the time the score of 5 or greater was reached. In a parallel cross-sectional analysis of 60 PwCF chosen at random from the total cohort, the relationship between sputum inflammatory mediators associated with disease progression in CF and CF-ABLE score was also evaluated. Changes in CF-ABLE scores over time in PwCF who commenced ivacaftor, double-combination therapy (DCT) with lumacaftor/ivacaftor or tezacaftor/