(vs 2.1 ± 2.0 μA/cm^2 for vehicle, $p < 0.001$, representing 48% restoration of wild-type CFTR Isc). CFTR inhibition with CFTR Inh-172 mirrored these responses. Monolayers demonstrated improved ASL (11.9 ± 4.9 μm ELX/TEZ/IVA vs 5.3 ± 2.5 μm 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 Isc correlated with augmented ASL with ELX/TEZ/IVA treatment (r = 0.74, $p < 0.001$). ELX/TEZ/IVA-treated Isc 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 Isc 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.

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

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Background: The advent of highly effective modulator therapies (HEMTs), including elexacaftor/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 ± 1.5 mm/min at baseline vs 4.0 ± 1.5 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.

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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 (FEV_1), 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/

ivacaftor, or triple-combination therapy (TCT) with elexacaftor/tezacaftor/ivacaftor were also recorded prospectively.

Results: In clinical practice, the CF-ABLE score performed substantially better than it did in its original derivation study and outperformed FEV_1 alone as a predictor of outcome. A CF-ABLE score of 5 or greater clearly distinguished PwCF who went on to poor outcomes from those who did not ($p < 0.001$). Approximately half of PwCF with a score of 5 or greater died or underwent lung transplantation within 4 years. In contrast, poor outcome at 4 years was observed in fewer than 5% of PwCF with a score less than 5. The score correlated with sputum neutrophil elastase activity; matrix metalloprotease activity; and interleukin (IL)-1β, IL-6, and IL-8 levels and inversely with IL-10 (all $p < 0.05$). For each mediator, the correlation with CF-ABLE score was stronger than with FEV_1 alone (all $p < 0.05$). In *F508del/F508del* PwCF, DCT did not result in better FEV_1 at 24 months than in matched controls not receiving DCT but significantly improved CF-ABLE score ($p = 0.002$), largely because of an effect on exacerbations. In contrast, TCT resulted in marked decreases in CF-ABLE score within 3 months ($p < 0.001$), enabling PwCF with baseline scores of 5 or greater to return to the low-risk range.

Conclusions: The CF-ABLE score robustly identifies PwCF at risk of poor outcome and correlates with airway inflammation better than FEV_1 alone. The score identifies a probable effect on mortality in response to CFTR modulators early in the treatment period – an endpoint that has proven elusive in prospective clinical trials and served as an obstacle in drug reimbursement negotiations with health care policymakers.

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A randomized controlled trial to determine the most sensitive outcome measure of airway clearance in cystic fibrosis

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Background: The best outcome measure for airway clearance in cystic fibrosis (CF) is unknown. Our National Institute for Health and Care Research–funded randomized controlled trial compared five primary outcome measures—sputum weight, forced expiratory volume in 1 second (FEV_1), end expiratory lung impedance (ΔEELI) from electronic impedance tomography, lung clearance index (LCI) from multiple-breath washout (MBW), R5-R20 from impulse oscillometry (IOS))—to determine the most sensitive measure of a single airway clearance session.

Methods: Subjects performed the outcome measures of MBW, IOS, and spirometry and were randomized to a single session of supervised airway clearance or rest for 30 minutes, after which MBW, IOS, and spirometry were repeated. Electronic impedance tomography and sputum were collected during the rest or airway clearance period. At a subsequent visit, the outcome measures were completed with the other intervention. Primary endpoint was difference in change in outcome measures before and after airway clearance or rest. Secondary endpoints included within-group treatment effect and other physiological parameters. Target sample size was 64 to allow subgroup analysis of two groups stratified according to percentage predicted FEV_1 (FEV_1pp) (>60%, ≤60%).

Results: Sixty-eight participants completed the study (42 male; mean age 41 ± 14.2; mean FEV_1pp 64.5 ± 23.9%). Sputum weight was significantly different after airway clearance (median change 4.4 g, interquartile range (IQR) 1.4–8.4 g) than after rest (median change 0 g, IQR 0–0.75 g) ($p < 0.05$). No other significant differences in primary outcome measures

Table 1 (abstract 157):
Change in primary outcome measures after airway clearance and rest for total study population and subgroups

Primary outcome measures	All participants (n = 68, except for LCI 2.5 where n = 62)			FEV1 > 60% Group (n = 33 for all OMs except LCI 2.5 where n = 31)			FEV1 ≤ 60% Group (n = 35 for all OMs except LCI2.5 where n =- 31)		
	Change after AC	Change after rest	Difference	Change after AC	Change after rest	Difference	Change after ACT	Change after rest	Difference
FEV_1 (litres) from spirometry			*p = 0.49*			*p = 0.79*			*p = 0.48*
Median	0	-0.01		0.01	0		0	0.01	
IQR	-0.05 - 0.04	-0.06 - 0.05		-0.04 – 0.05	-0.07 - 0.04		-0.03 – 0.03	-0.04 – 0.07	
95% CI	-0.02 – 0.02	-0.03 – 0.01		-0.03 – 0.05	-0.05 – 0.03		-0.02 – 0.02	-0.01 – 0.04	
FEV_1 %pred (%) from spirometry			*p = 0.17*			*p = 0.79*			*p = 0.22*
Median	0	0		-0.01	0		0	0	
IQR	-0.01 - 0.01	-0.02-0.01		-0.05 - 0.04	-0.04 - 0.07		-0.01 – 0.01	-0.02 – 0.01	
95% CI	0-0	-0.01 – 0		-0.05 – 0.03	-0.03 – 0.05		0 – 0.01	-0.01 - 0	
LCI 2.5 from MBW			*p = 0.53*			*p = 0.87*			*p = 0.34*
Median	-0.18	-0.12		-0.19	-0.11		-0.09	-0.12	
IQR	-0.81 - 0.68	-0.84 - 0.37		-0.55 – 0.36	-0.83 – 0.35		-0.91 – 0.88	-1.22 – 0.52	
95% CI	-0.4 – 0.4	-0.4 – 0.1		-0.36 – 0.31	-0.73 – 0.09		-0.76 – 0.77	-0.84 – 0.20	
R5-R20 (kPasL-1) from IOS			*p = 0.51*			*p = 0.17*			*p = 0.82*
Median	0	0		-0.01	0		0	-0.01	
IQR	-0.01 - 0.02	-0.02 - 0.02		-0.02 – 0	-0.02 – 0.01		-0.03 – 0.02	-0.03 - 0.02	
95% CI	0 – 0.01	0 – 0.01		-0.01 - 0	-0.01 – 0.01		-0.01 – 0.02	-0.02 – 0.01	
ΔEELI from EIT			*p = 0.21*			*p = 0.65*			*p = 0.19*
Median	933.04	55.93		-1857.8	-713.42		-652.82	742.35	
IQR	-1285.70 - 3611.41	-4255.4 - 1399.46		-12273 – 2066.31	-1823.7 – 5123		-2588.48 – 1056.18	-1139.91 – 3387.8	
95% CI	282.8 – 1873.7	-1198.8 – 724.9		-3298.6 - -87.9	-1403.1 – 1315.6		-1251.0 – 156.3	-455.0 – 1923.5	
Sputum Weight (grams)			*p <0.005 **			*p<0.005**			*p<0.005**
Median	4.4	0		3.9	0		5.8	0	
IQR	1.4 - 8.4	0 - 0.75		1.6 – 6.5	0 – 0.8		1.1 – 9.80	0 – 0.60	
95% CI	3.6 – 6.1	0 – 0.4		3.0 – 6.1	0 -0.7		2.6 – 8.4	0 – 0.4	

*** = Statistically significant difference.**
P-values calculated using Wilcoxen Signed Rank tests
95% CI's derived from medians