analysis. Data collection for the 144-week interim analysis was based on the date the last participant reached at least Week 144 (Extended Week 144).
Results: 506 participants (*F508del*/minimal function [*F*/MF] genotypes, n = 399; *F508del*/ *F508del* [*F*/*F*] genotype, n = 107) were enrolled and dosed. At the 144-week interim analysis, mean (SD) exposure to ELX/TEZ/IVA was 151.1 (33.7) weeks. Overall, 99% of participants had an adverse event (AE), which for most were mild (16.4%) or moderate (60.3%) in severity. The overall exposure-adjusted rates of AEs and serious AEs (586.55 and 22.42 events per 100 patient years) were lower compared with the 24-week pivotal study that formed the basis of the ELX/TEZ/IVA safety profile (1096.01 and 36.93 events per 100 patient years). Fourteen patients (2.8%) had AEs that led to treatment discontinuation. In participants with *F*/MF genotypes, mean (SE) absolute changes in $ppFEV_1$ from parent study baseline at Extended Week 144 were 14.8 (0.8; n = 161) and 14.1 (0.8; n = 166) percentage points in those originally assigned to placebo and ELX/TEZ/IVA in the parent study, respectively. The estimated PEx rate (95% CI) per 48 weeks was 0.20 (0.16, 0.24); in the parent study, the estimated PEx rate per 48 weeks was 0.98 for the placebo group. In participants with the *F*/*F* genotype, mean (SE) absolute changes in $ppFEV_1$ from parent study baseline at Extended Week 144 were 12.0 (1.3; n = 44) and 11.6 (1.2; n = 48) percentage points in those assigned to the TEZ/IVA and ELX/TEZ/IVA groups in the parent study, respectively. The estimated PEx rate (95% CI) per 48 weeks was 0.18 (0.12, 0.26). The absolute changes in sweat chloride and CFQ-R respiratory domain score with ELX/TEZ/IVA treatment were comparable to those seen in the parent studies. The mean annualized rate of change in $ppFEV_1$ was 0.07 (−0.12, 0.26) for all participants..
Conclusions: ELX/TEZ/IVA continued to be generally safe and well tolerated, with no new safety findings. The clinically meaningful improvements in lung function, respiratory symptoms, and CFTR function reported in the parent studies were maintained through Week 144 of this extension study..
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172

Treatment changes and outcomes in adults taking elexacaftor/tezacaftor/ivacaftor at two years: A single-center experience

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Background: Approval of the highly effective cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapy elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in 2019 has substantially improved the overall health of people with CF (PwCF), with some PwCF taking ELX/TEZ/IVA able to change their chronic daily therapies after starting treatment. In this retrospective observational study, we aimed to understand the clinical characteristics of individuals who changed chronic daily therapies and the effects of these changes on clinical outcomes at 2 years.
Methods: We conducted a single-center study at the Indiana University Adult Cystic Fibrosis Center between January 1, 2020, and March 12, 2020. Our study included patients who had been on ELX/TEZ/IVA for a minimum of 60 days and were performing daily airway clearance with oscillating positive expiratory pressure or high-frequency chest wall oscillation or using one or more of the following respiratory medications: dornase alfa, hypertonic saline, or inhaled antibiotics. During follow-up, patients were queried about whether they had made any changes to their chronic daily therapy since initiating ELX/TEZ/IVA. Data recorded included age, sex at birth, mutation type, body mass index, baseline forced expiratory volume in 1 second (FEV_1), quality of life, prior modulator therapy, and history of difficulty sustaining daily care. Clinical outcomes were determined 1 and 2 years after starting ELX/TEZ/IVA therapy based on FEV_1, hospitalizations, and additional changes to chronic daily therapies, including resumption of previously discontinued therapy. Data were analyzed using paired two-tailed t-tests.
Results: During the period of interest, 85 individuals (50.1% female) were seen. Mean participant age was 30.0 ± 9.6. At the first follow-up visit, 36% of patients had died or stopped chronic respiratory medication or airway clearance (Figure 1). Patients who changed therapy were older (32.5 ± 10.8 vs 28.5 ± 8.4, $p = 0.06$), had greater change in FEV_1 (12.2 ± 8.3% vs 7.1 ± 6.3%, $p = 0.002$), and had a large but insignificant change in the Cystic Fibrosis Questionnaire-Revised respiratory domain (31.4 ± 17.4 vs 23.9 ± 20.4, $p = 0.18$) than those who did not. Thirty-eight percent of individuals who discontinued treatment at the first visit and 39% of those who did not modify therapy made further changes to therapy at 1-year follow-up. Only 17% of patients who had previously discontinued treatments had resumed one or more therapies at 1-year follow-up. Of individuals who made changes to their chronic therapy and had a hospitalization in the year before initiating ELX/TEZ/IVA, 63% had no hospitalization at 1-year follow-up. No significant changes in lung function were seen after stopping chronic daily therapies.

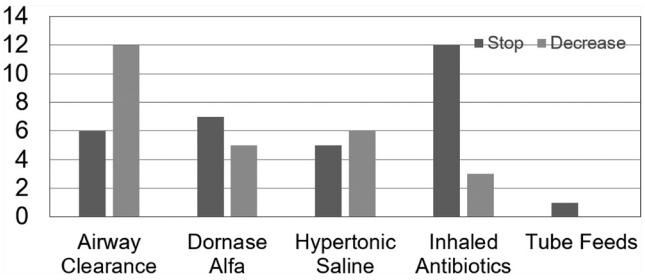

Figure 1. Number of individuals who reported modified chronic daily therapies at the first visit

Conclusions: In a single-center, retrospective observational study, more than one-third of PwCF decreased their chronic daily therapies after initiating ELX/TEZ/IVA. No adverse effects on lung function or hospitalizations were noted. Larger studies are needed to determine the safety of discontinuation of chronic daily respiratory therapies after starting ELX/TEZ/IVA.

173

Effectiveness of elexacaftor/tezacaftor/ivacaftor in children with cystic fibrosis: The pediatric PROMISE study

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Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator combination approved for children with CF aged 6 and older with at least one ELX/TEZ/IVA-responsive CFTR allele. Efficacy and safety in children aged 6 to 11 were assessed in one open-label and one placebo-controlled Phase 3 trial. The PROMISE study is an ongoing U.S. multicenter, observational, prospective cohort study examining efficacy in the post-approval "real world" setting in people with CF prescribed ELX/TEZ/IVA clinically. Here we report preliminary 1-month follow-up data from the Pediatric Substudy in children aged 6 to 11.
Methods: Key eligibility criteria included a diagnosis of CF, at least one ELX/TEZ/IVA-responsive CFTR variant, and aged 6 to <11 at ELX/TEZ/IVA initiation. The primary outcome was change in lung clearance index (LCI) according to multiple-breath washout. Secondary outcomes reported here include changes in percentage predicted forced expiratory volume in 1 second (FEV_1pp), sweat chloride, and Cystic Fibrosis Questionnaire-Revised

Table 1 (abstract 173):
Changes in lung clearance index (LCI), percentage predicted forced expiratory volume in 1 second (ppFEV$_1$), sweat chloride (SwCl), and the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) from baseline to 1 month after initiation of elexacaftor/tezacaftor/ivacaftor

Outcome	Visit	n	Mean ± SD	Change (95% CI)
LCI(2.5)	Baseline, pre-ETI	94	7.25 ± 1.27	
	1 month post-ETI	96	6.55 ± 0.74	-0.82 (-1.10, -0.54)
ppFEV1	Baseline, pre-ETI	124	99.9 ± 14.1	
	1 month post-ETI	118	104.8 ± 13.9	+4.97 (3.04, 6.90)
SwCl	Baseline, pre-ETI	102	87.0 ± 25.6	
	1 month post-ETI	99	42.3 ± 16.5	-44.9 (-48.4, -41.3)
CFQ-R	Baseline, pre-ETI	124	86.3 ± 10.4	
	1 month post-ETI	117	89.9 ± 10.9	+3.76 (1.70, 5.82)

(CFQ-R) respiratory domain score. Changes from baseline to 1-month follow-up were analyzed using a paired t-test on a complete-case cohort.
Results: Of 125 participants at 20 sites enrolled in the Pediatric Substudy, 119 had completed the 1-month visit at the time of analysis. Mean age at initiation of ELX/TEZ/IVA was 9.2 ± 1.8 years, and 44% were female at birth. There were 65 (52%) F508del homozygous participants, 34 (27%) F508del heterozygous participants with a minimal-function second allele, and 26 (21%) participants with other CFTR variants (heterozygotes with gating or residual function second alleles or no F508del alleles). Results at baseline and 1 month and change (mean, 95% CI) are reported in Table 1. LCI, FEV$_1$pp, sweat chloride, and CFQ-R respiratory domain score all improved significantly from baseline to the 1-month visit.
Conclusions: In this ongoing, prospective, observational postapproval study of ELX/TEZ/IVA in children, preliminary results at 1-month follow-up indicate significant improvements in LCI, FEV$_1$pp, sweat chloride, and self-reported respiratory symptoms. At this interim analysis, the magnitude of change for all outcome measures was lower than reported in the Phase 3 clinical trials in this age range, although baseline lung function was better in the current study—similar to what has been observed for the PROMISE study in subjects aged 12 and older [1]. Future reports will evaluate a broader range of endpoints for up to 4 years.
Acknowledgements: Funded by the Cystic Fibrosis Foundation.

Reference

[1] Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, *et al.*; PROMISE Study group. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: A clinical trial. *Am J Respir Crit Care Med* 2022;205(5):529–539. https://doi:10.1164/rccm.202108-1986OC.

174

Identification of physiological characteristics at baseline and 1 and 6 months that segregate lung function response to ivacaftor using proteomic analysis

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Background: Ivacaftor targets abnormal gating of the cystic fibrosis (CF) transmembrane conductance regulator (CFTR). The G551D Observational (GOAL) study is a longitudinal observational cohort of patients with at least one G551D mutation starting ivacaftor. Six months after drug initiation, there was a mean change in percentage predicted force expiratory volume in 1 second (FEV$_1$pp) of 6.7% (95% CI, 4.9–8.5%) and a mean decline in sweat chloride of 54 mEq (95% CI, −57.7 to −49.9 mEq), although approximately half of study participants who exhibited physiologic CFTR modulation (sweat chloride change of −80 to −60 mEq/L) did not have improvement in FEV$_1$. The aim of this study was to understand the biological basis for lack of lung function response to modulator therapy.
Methods: Plasma samples were obtained from GOAL study participants with baseline FEV$_1$pp of 64% to 84% and sweat chloride change at 6 months of −80 mEq/L to −60 mEq/L. Samples were blinded, randomized, albumin depleted, fractionated, and subjected to mass spectrometry proteomics. Samples from lung function responders, with an increase in FEV$_1$pp of 5% or more at 1 and 6 months (baseline n = 15, 1 month n = 15, 6 months n = 14), were compared with those of nonresponders, with change in FEV$_1$pp of less than 5% at 1 and 6 months (baseline n = 27, 1 month n = 15, 6 months n = 15).
Results: At baseline, using standard stringency filters on the data, we identified 2,820 protein isoform differences between lung function nonresponders and responders. Pathway analysis of these proteins identified enrichment for wound healing ($p < 0.001$), cellular organization ($p < 0.001$), and cell migration ($p < 0.001$) (Figure 1). One month after ivacaftor initiation, there were 1,267 protein differences that continue to be associated with cellular organization ($p < 0.001$) and new associations with regulation of smooth muscle contraction ($p < 0.001$), catecholamines ($p = <0.001$), and nitrogen compound metabolic process ($p < 0.001$). Six months after ivacaftor initiation, there were 1,757 protein isoform differences that continued to be associated with cellular organization ($p < 0.001$) and migration ($p = 0.001$). High-stringency filtering of the data identified alterations in ciliary movement ($p < 0.001$), inflammation ($p < 0.001$), and remodeling ($p < 0.001$) as segregators of 6-month response at baseline. At 1 month, application of high-stringency filters to the data identified differences in interleukin-18-mediated signaling ($p = 0.001$). At 6 months, the high-stringency filters identified inflammation ($p < 0.001$), positive regulation of nitrogen compound metabolic process ($p < 0.001$), and negative regulation of nitrogen compound metabolic process ($p < 0.001$).