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.

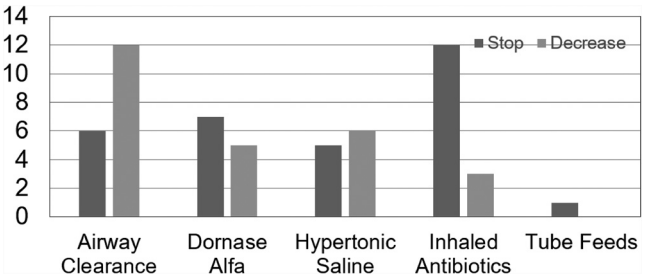

Figure 1. Number of individuals who reported modified chronic daily therapies at the first visit

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