Methods: APPLAUD was a double-blind, placebo-controlled study in adults with CF, randomized (1:1) to LAU-7b or placebo for six consecutive treatment cycles of 21 days separated by 7-day drug-free periods. Eligible subjects had a percentage predicted forced expiratory volume in 1 second (FEV_1pp) between 40% and 100% at screening and had had at least one pulmonary exacerbation (PEx) in the prior year. The study drug was administered orally once daily, in addition to standard of care. The primary efficacy endpoint was absolute change from baseline in FEV_1pp at 24 weeks. Secondary endpoints included parameters related to PEx, quality of life, and systemic inflammatory and lipidomic biomarkers.
Results: One hundred sixty-six subjects from 40 sites in the United States, Canada, and Australia were randomized. Preliminary results showed that absolute change in FEV_1pp at 24 weeks was 0.8 points in favor of LAU-7b (-0.8 FEV_1pp change from baseline in the LAU-7b arm, n = 83, versus −1.6 FEV_1pp in the placebo arm, n = 83; $p = 0.43$). Planned stratification factor analysis showed that subjects with FEV_1pp of 70% or greater at baseline responded better, resulting in a treatment difference of 3.0 points in FEV_1pp at 24 weeks favoring LAU-7b (-0.9 FEV_1pp change from baseline in the LAU-7b arm, n = 29, versus −3.9 FEV_1pp in the placebo arm, n = 27; $p = 0.06$). Although the number of subjects was small, similar positive trends were noted in subjects already treated with CFTR modulators, including elexacaftor/tezacaftor/ivacaftor. PEx incidence and number of days of intravenous antibiotics were lower in the LAU-7b than the placebo arm. The safety profile of LAU-7b treatment was consistent with the safety profile observed in previous clinical studies with fenretinide. Serious adverse events and their severity and relationship distribution were similar between the two treatment arms, with no unexpected serious adverse reaction or deaths reported.
Conclusions: Compared to placebo, LAU-7b treatment reduced loss of lung function by 50% at 24 weeks in the overall subject population and by 77% in the subgroup of subjects with mild lung disease (FEV_1pp≥70%), suggesting a potential beneficial effect on the loss of lung function over 24 weeks. LAU-7b was well tolerated and had a favorable safety profile, similar to previously obtained data. The final efficacy data, including inflammation biomarker analyses, will be presented at the North American Cystic Fibrosis Conference.
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169

A phase 4, fully decentralized clinical trial to evaluate physical activity and cough frequency in patients with cystic fibrosis using wearable technology

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Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been approved for use in people with cystic fibrosis (CF) aged 6 and older with one or more *F508del-CFTR* mutations or another ELX/TEZ/IVA-responsive mutation. Here we report results from a Phase 4, fully decentralized pilot study designed to evaluate the performance of wearable technology in assessing physical activity and cough frequency in people with CF aged 18 and older treated with commercial ELX/TEZ/IVA (NCT04923464).
Methods: Wearable devices were used to measure daily physical activity and cough frequency over a 12-week measurement period. Participants, who had been taking commercial ELX/TEZ/IVA for at least 4 weeks before screening, were provided with a wrist-worn actigraphy sensor (worn continuously during the measurement period) and an ambulatory cough monitoring system (worn once per week for 24 continuous hours). The primary endpoint was compliance with the actigraphy device (defined as percentage of time wearing device during measurement period). Secondary endpoints included compliance with the cough measurement device (defined as percentage of time wearing device during 24-hour measurement period each week, averaged over 12 weeks), number and variability of steps per day, and number and variability of coughs per day.
Results: Fifty-one participants were enrolled (mean age 34.6 ± 11.6; mean percentage predicted forced expiratory volume in 1 second (FEV_1pp) at screening 68.8 ± 23.0%). Five participants discontinued the study (adverse event [skin reaction from device adhesive], n = 1; withdrawal of consent not due to adverse event, n = 2; other reasons, n = 2). Mean compliance was 91.3% with the actigraphy device and 84.8% with the cough measurement device. During the 12-week measurement period, mean step count ranged from 4,400 to 5,500 steps per day (standard deviation 2,300–3,000 steps/day), and geometric mean cough count ranged from 21 to 33 coughs per day (standard deviation 4.1 to 7.0 coughs per day).
Conclusions: Overall, compliance was high for use of the actigraphy sensor and ambulatory cough monitoring system. The variability observed in step counts and cough counts obtained from these wearable devices was generally consistent with previous reports. Cough counts for these participants stable on ELX/TEZ/IVA were comparable with reported counts for healthy adults. These results show that performing fully decentralized trials in people with CF using wearable technology is feasible and indicate the potential for such trials to provide novel clinical insights into CF disease progression and the efficacy of CF transmembrane conductance regulator modulators.
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170

Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one *F508del* allele: 144-week interim results from an open-label extension study

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Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was shown to be efficacious and safe in participants aged 12 years and older with cystic fibrosis (CF) and at least one *F508del-CFTR* allele in two pivotal Phase 3 trials. A 192-week Phase 3, open-label extension study is being conducted to assess long-term safety and efficacy in these participants. Here, we report results of the 144-week interim analysis.
Methods: Participants are receiving ELX 200 mg once daily/TEZ 100 mg once daily/IVA 150 mg every 12 hours. The primary endpoint is safety and tolerability; secondary endpoints include absolute changes from parent study baseline in percentage predicted FEV_1 ($ppFEV_1$), sweat chloride, Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, and body mass index and number of pulmonary exacerbations (PEx). Annualized rate of change in $ppFEV_1$ was assessed as a pre-planned ad hoc

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.

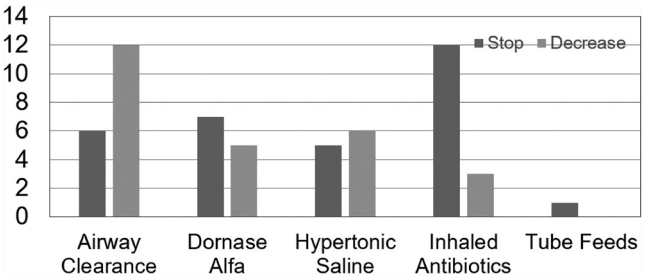

Figure 1. Number of individuals who reported modified chronic daily therapies at the first visit

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