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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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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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