

**Figure 1.** Preliminary medication possession ratio (MPR) data before and after introduction of elexacaftor/tezacaftor/ivacaftor and Medication Electronic Monitoring System (MEMS) data for overall adherence at 12 months

**Conclusions:** ELX/TEZ/IVA adherence may be overestimated in SRQ and MPR data. Adherence to routine CF therapies is poor, and initiation of ELX/TEZ/IVA may contribute to further reductions with some treatments. Data collection is ongoing for this cohort. Additional data will be available for presentation at the conference.

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### Two-year respiratory culture and pulmonary function outcomes in patients on elexacaftor/tezacaftor/ivacaftor

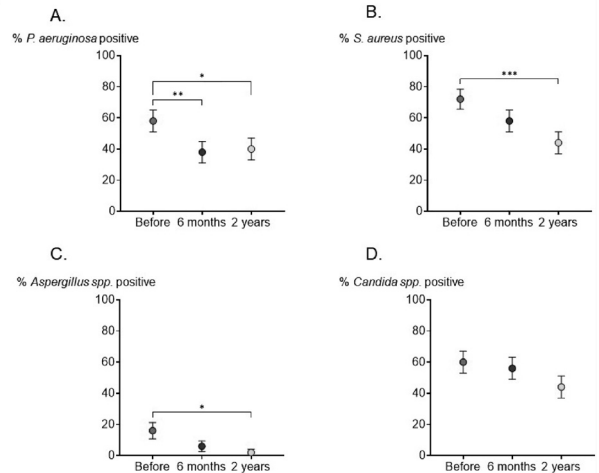
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**Background:** Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), a combination cystic fibrosis (CF) transmembrane conductance regulator modulating medicine, has been widely available to patients in the United States for the past 2 to 3 years. Multiple studies have reflected the improvement in respiratory symptoms and measurements that clinicians have noted while caring for these patients. Previous modulator therapies found similar improvements in respiratory measurements, yet patients were found to have return of baseline *Pseudomonas aeruginosa* densities at 2 years [1]. We investigated whether similar findings would occur with ELX/TEZ/IVA therapy after 2 years and whether improvements in pulmonary function testing measurements would persist as well.

**Methods:** A retrospective, single-center study was performed using patient data from the adult CF program at the University of Missouri. Fifty patients were included in the analysis, with each patient having completed a pulmonary function test and respiratory culture before and after starting therapy with ELX/TEZ/IVA and again approximately 2 years later.

**Results:** Significant improvement was found in percentage predicted forced expiratory volume in 1 second (FEV<sub>1</sub>pp), percentage predicted forced vital capacity (FVCpp), and absolute change in forced expiratory volume in 1 second (FEV<sub>1</sub> L) and forced vital capacity (FVC L) soon after starting ELX/TEZ/IVA, as well as continued improvement at 2 years in FEV<sub>1</sub>pp (mean difference 95% CI, 0.24–5.75,  $p=0.03$ ) and FVCpp (mean difference 95% CI, 2.6–7.76,  $p<0.001$ ). There was a significant reduction in percentage of positive respiratory cultures for *P. aeruginosa* soon after starting ELX/TEZ/IVA that persisted at 2 years (mean difference 95% CI, –3.05 to –32.95,  $p=0.01$ ) (Figure 1A). Unlike *P. aeruginosa*, the percentage of positive respiratory cultures for *Staphylococcus aureus* was not significantly different soon after starting therapy but was found to be significantly lower at 2 years (mean difference 95% CI, –12.5 to –43.5,  $p<0.001$ ) (Figure 1B). Like *S. aureus*, a significant reduction in percentage of positive respiratory cultures for *Aspergillus* species was found at 2 years that was not seen right after starting therapy (mean difference 95% CI, –2.02 to –25.98,  $p=0.02$ ) (Figure 1C). No significant difference was noted at 2 years in cultures positive for *Candida* species after starting ELX/TEZ/IVA, although a trend toward significance was found at 2 years despite most cultures being obtained via throat swab cultures (before vs 2 years, mean difference 95% CI 3.5 to –39.5,  $p=0.12$ ) (Figure 1D).

Figure 1



**Figure 1.** Percentage of respiratory cultures positive for (A) *Pseudomonas aeruginosa*, (B) *Staphylococcus aureus*, (C) *Aspergillus* spp., and (D) *Candida* spp. before, 6 months after, and 2 years after starting elexacaftor/tezacaftor/ivacaftor

**Conclusions:** Unlike previously seen return-to-baseline bacterial colonization densities at 2 years with early modulator therapies, patients at our center continue to have a reduction in percentage positive respiratory cultures for *S. aureus*, *P. aeruginosa* and *Aspergillus* species 2 years after starting ELX/TEZ/IVA. Continued improvement in pulmonary function testing measurements were also found at 2 years, warranting further investigation.

### Reference

- [1] Kidd T. *Pseudomonas aeruginosa* infection after CFTR restoration. One step back, one step forward. *Am J Respir Crit Care Med* 2017;195:1550–1552.

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### Results from APPLAUD phase 2 study with pro-resolution drug candidate LAU-7b in adults with cystic fibrosis

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**Background:** LAU-7b (oral fenretinide) is a novel drug candidate that acts on membrane lipids to modulate inflammation signaling and protein trafficking. Membrane lipid imbalance is believed to play a role in aberrant pulmonary inflammation in individuals with cystic fibrosis (CF), leading to irreversible lung damage over time. Fenretinide was shown to correct the levels of certain membrane phospholipids and sphingolipids in multiple in vitro and in vivo models of CF, improving resolution of inflammation and increasing functional CFTR expression, even under cellular stress conditions. A phase 2 clinical trial (APPLAUD) was conducted in adults with CF to evaluate the safety of LAU-7b and its effect on preservation of lung function by reducing inflammation and restoration of homeostasis.

**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<sub>1</sub>pp) 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<sub>1</sub>pp 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<sub>1</sub>pp at 24 weeks was 0.8 points in favor of LAU-7b (-0.8 FEV<sub>1</sub>pp change from baseline in the LAU-7b arm, n = 83, versus -1.6 FEV<sub>1</sub>pp in the placebo arm, n = 83; p = 0.43). Planned stratification factor analysis showed that subjects with FEV<sub>1</sub>pp of 70% or greater at baseline responded better, resulting in a treatment difference of 3.0 points in FEV<sub>1</sub>pp at 24 weeks favoring LAU-7b (-0.9 FEV<sub>1</sub>pp change from baseline in the LAU-7b arm, n = 29, versus -3.9 FEV<sub>1</sub>pp 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 elxacaftor/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<sub>1</sub>pp ≥ 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<sub>1</sub>pp) 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 elxacaftor/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<sub>1</sub> (ppFEV<sub>1</sub>), 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<sub>1</sub> was assessed as a pre-planned ad hoc