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Elexacaftor/tezacaftor/ivacaftor reduces trapped gas in children with cystic fibrosis

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Background: Mucus plugging, one of the features of early cystic fibrosis (CF) pathophysiology, can lead to poorly ventilated areas in the lung that are incompletely emptied during tidal breathing. The volume of gas retained within these lung units is referred to as trapped gas and can be assessed using different modalities such as multiple-breath washout (MBW) and functional imaging. During MBW, the volume of trapped gas (VTG) can be quantified by adding a series of inspiratory capacity breaths at the end of a standard nitrogen (N_2) MBW test to recruit lung regions that release residual N_2 [1]. VTG has been shown to be high in CF, but it is unknown whether VTG captures changes after elexacaftor/tezacaftor/ivacaftor.

Methods: This is a single-center add-on study of participants enrolled in one of two ongoing studies: the multi-center HyperPOlarized Imaging of New Therapies (HyPOINT, NCT04259970) study and a SickKids-based observational study of participants initiated on CF transmembrane conductance regulator (CFTR)-modulator treatment. In this study protocol, the following tests were performed at baseline and 1 month after start of elexacaftor/tezacaftor/ivacaftor. N_2 MBW was performed using the ExhalyzerD MBW device and Spiroware 3.3.1 software (EcoMedics, Duernten, Switzerland). Lung clearance index (LCI) and VTG were reported, with VTG expressed as percentage of forced vital capacity measured using spirometry (VTG/FVC%). Hyperpolarized ^{129}xenon magnetic resonance imaging (Xe-MRI) and free-breathing MRI were also performed at each visit for participants enrolled in the HyPOINT study. Using the Phase Resolved FUnctional Lung (PREFUL) method, fractional ventilation (FV) maps were determined from free-breathing images [2]. Ventilation defect percentage (VDP) was calculated from Xe-MRI ventilation images (VDP_{Xe}) based on a threshold of 60% of the mean ventilation signal and FV maps (VDP_{FV}) using k-means clustering [2]. Statistical analysis included Wilcoxon rank sign test for before and after comparisons and Spearman test for correlations.

Results: Ten participants (median age 16.2, range 13.5–18.6), have completed MBW at both visits; recruitment is ongoing. At baseline, median LCI was 9.66 (range 6.22–16.08) and percentage predicted forced expiratory volume in 1 second (FEV_1pp) was 73% (43–95%). Across the two visits, median LCI decreased from 9.66 (interquartile range (IQR) 7.43–11.39) to 7.73 (IQR 6.51–8.91) ($p = 0.04$), and FEV_1pp increased from 72% (IQR 66–80%) to 88% (IQR 78–99%). VTG/FVC% decreased from 3.47% (IQR 2.40–6.23%) to 1.36% (IQR 0.89–3.61%) ($p < 0.01$). Relative difference in VTG/FVC% correlated with relative change in VDP_{Xe} ($r = 0.71$, $p = 0.05$, Figure 1A) and with VDP_{FV} ($r = 0.86$, $p < 0.01$, Figure 1B).

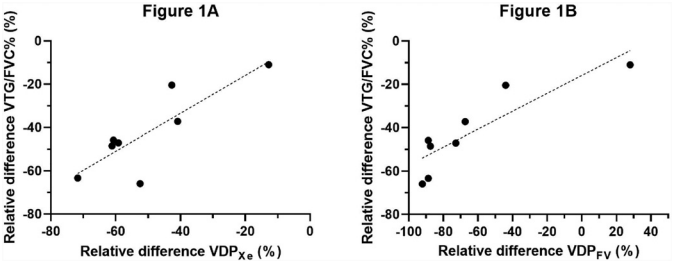

Figure 1. Correlation between relative difference in volume of trapped gas expressed as percentage of forced vital capacity measured using spirometry (VTG/FVC%) and A) relative difference in ventilation defect percentage (VDP) calculated from ^{129}xenon magnetic resonance imaging ventilation images and B) relative difference in VDP fractional ventilation maps

Conclusions: Trapped gas, measured according to VTG/FVC% during MBW, decreases after initiation of highly effective CFTR modulator therapy and correlates well with changes measured using functional MRI.

Acknowledgements: The Cystic Fibrosis Foundation supported this work.

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Acceptability and usability of a soft, flexible, wearable device for cough detection in children with cystic fibrosis

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Background: Cough is a common symptom in cystic fibrosis (CF), and an increase in cough is an important sign of worsening lung disease and pulmonary exacerbation, the most common cause of hospitalization in people with CF. Objective monitoring of cough could be an important outcome measure for clinical trials, especially in children too young to perform pulmonary function tests. There are no accurate, objective methods of quantifying the frequency, severity, and duration of cough. Devices that have been tested to measure cough are neither highly reliable nor user friendly. We developed a mechano-acoustic sensor (MAS): a 4.8-cm- × 2.8-cm- (1 inch) long, thin, lightweight, stretchable, wireless device that adheres easily and securely to the skin surface and is worn at the base of the neck. The device was validated in adults being monitored for COVID-19. This study evaluated usability and acceptability to children and their parents.

Methods: In Cohort 1, a small, flexible, fully wireless accelerometer-based MAS was applied to the suprasternal notch of children with CF using gentle adhesives. Participants were asked to perform activities that included forced coughs while sitting, lying down, and performing activities such as jumping or jogging and other pharyngolaryngeal activities such as swallowing, speaking, and throat clearing. The sessions were an average of about 30 minutes long. In Cohort 2, participants were asked to test the device for a longer period of wearable time (4–6 hours) in various settings, including outpatient clinics, inpatient rooms, and outside clinic and at-home environments. Upon completion, all participants from both cohorts

were asked to fill out the Acceptability and Usability Questionnaire, which consisted of six questions ranked on a 4-point Likert scale.
Results: Cohort 1 included 21 children aged 3 to 18 (mean age 9.25 ± 4.85), and Cohort 2 included 12 children aged 7 to 18 (mean age 12.15 ± 4.42). On 31 (94%) questionnaires returned, 35.5% of participants strongly agreed and 61.3% agreed with the statement "I [or my child] like(s) wearing the cough sensor." Similarly, most participants found the cough sensor easy to use (74.2% strongly agreed, 25.8% agreed) and comfortable to wear (64.5% strongly agreed, 29.0% agreed), although they found the adhesive sticker difficult to take off and the device too obvious or large.
Conclusions: Although qualitative and quantitative acceptability and usability data were overall positive, we have redesigned the cough sensor for comfort and are continuing enrollment. The new sensor, 3.5 × 1.6 × 0.8 cm, is smaller and sits lower on the neck so participants can better conceal it underneath clothing (Figure 1). We are providing universal adhesive remover wipes to all participants. Future work includes long-term monitoring (1–2 weeks) of pulmonary exacerbations using the new devices and further assessing usability and acceptability from participants.

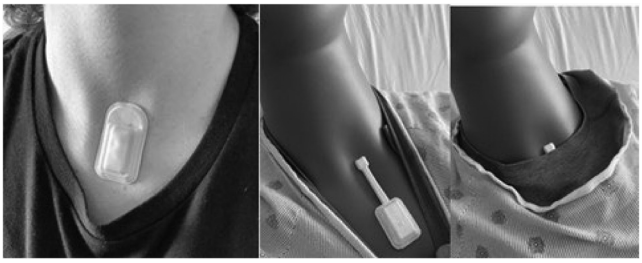

Figure 1. New cough sensor design with a longer neck and a smaller body, allowing it to be better concealed underneath a shirt

Acknowledgements: Cystic Fibrosis Foundation MCCOLL20A0-I.

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Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in children 6 years and older with cystic fibrosis and at least one *F508del* alleles: 96-week interim results from an open-label extension study

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Background: A 24-week, Phase 3 open-label study showed that elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was safe and efficacious in children 6 through 11 years of age with cystic fibrosis (CF) and at least one *F508del-CFTR* allele. All children who completed this trial entered a 192-week, Phase 3, open-label extension study to assess long-term safety and efficacy. Here, we report results of the 96-week interim analysis (IA).
Methods: Dosing in the study is based on weight. Children who weigh less than 30 kg receive ELX 100 mg once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h), while children weighing 30 kg or more receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (adult dose). The primary endpoint is safety and tolerability; secondary endpoints include absolute changes from parent study baseline in percent predicted FEV_1 ($ppFEV_1$), sweat chloride, Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, body mass index, body mass index z-score, lung clearance $index_{2.5}$ ($LCI_{2.5}$), weight and weight-for-age z score, and height and height-for-age z-score and number of pulmonary exacerbations (PEx) and CF-related hospitalizations. Data collection for the 96-week IA was based on the date the last participant completed the Week 96 study visit.
Results: 64 children (*F508del*/minimal function [*F*/MF] genotypes, n = 36; *F508del*/*F508del* [*F/F*] genotype, n = 28) were enrolled and dosed. At the 96-week IA, mean (SD) exposure to ELX/TEZ/IVA was 93.9 (11.1) weeks. Adverse events (AEs) and serious AEs (SAEs) were consistent with common manifestations of CF disease. The overall exposure-adjusted rates of AEs and SAEs (407.74 and 4.72 events per 100 patient years) were lower compared with the 24-week parent study (987.04 and 8.68 events per 100 patient years). One child (1.6%) discontinued due to an AE of aggression, which was moderate in severity and considered unlikely to be related to the study drug. From parent study baseline to Week 96, mean $ppFEV_1$ increased (11.2 [95% CI, 8.3, 14.2] percentage points), sweat chloride concentration decreased (-62.3 [95% CI, -65.9, -58.8] mmol/L), CFQ-R respiratory domain score increased (13.3 [95% CI, 11.4, 15.1] points), and $LCI_{2.5}$ decreased (-2.00 [95%, -2.45, -1.55] units). Improvements were also seen in growth parameters. The estimated PEx rate per 48 weeks was 0.04. The annualized rate of change (95% CI) in $ppFEV_1$ and $LCI_{2.5}$ was 0.51 (-0.73, 1.75) percentage points and -0.06 (-0.17, 0.05) units, respectively.
Conclusions: ELX/TEZ/IVA continued to be generally safe and well tolerated in children 6 through 11 years of age through an additional 96 weeks of treatment, with no new safety findings. Improvements in lung function, respiratory symptoms, and CFTR function reported in the parent study were maintained through the interim analysis of this extension study. These results demonstrate the favorable safety profile and durable clinical benefits of ELX/TEZ/IVA treatment in this pediatric population.
Acknowledgements: This work was funded by Vertex Pharmaceuticals Incorporated.

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Tolerance of ETD001, a long-acting inhaled epithelial sodium channel blocker, in humans

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Background: To assess the safety, tolerability, and pharmacokinetic (PK) profile in humans of the novel inhaled epithelial sodium channel blocker ETD001.
Methods: Inhaled ETD001 or placebo, delivered via nebulizer, have been administered in a 3:1 ratio to 96 healthy subjects in a blinded, first-in-human clinical trial (ClinicalTrials.gov Identifier: NCT04926701). The study consisted of two parts. Part A evaluated single ascending doses (SADs) up to 10.8 mg, and Part B evaluated multiple ascending doses (MADs) up to 3.1 mg once daily (QD) for 7 days and 4.65 mg twice daily (BID) for 14 days. Safety was assessed by monitoring for adverse events (AEs), laboratory safety tests (including blood potassium monitoring), vital signs, 12-lead electrocardiogram (ECG), and spirometry. Systemic exposure was assessed using serial pharmacokinetic blood draws.
Results: There were no serious AEs. Twenty-four subjects reported 38 AEs, all of mild to moderate intensity and all resolved. There were no clinically relevant changes in laboratory safety tests, vital signs, ECGs, or spirometry measurements. All blood potassium assessments were within normal range at all doses. Three subjects withdrew in Part B; all withdrawals were considered unrelated to study drug: one on day 6 from the 3.1-mg QD cohort for personal reasons, one after the first dose of the 3.1-mg BID cohort because of vasovagal syncope at time of venipuncture triggering atrial fibrillation that spontaneously resolved, and one on Day 4 of the 3.1-mg BID cohort because of a positive COVID-19 test. Pharmacokinetic parameters were approximately dose proportional in Part A, with peak concentrations 1 to 2 hours after dose and exposure out to 12 to 24 hours at all doses, indicating good lung retention. Part B plasma concentrations displayed dose-independent kinetics and showed minimal accumulation, with a mean of 1.11-fold observed over 14 days.
Conclusions: ETD001 was well tolerated at single doses up to 10.8 mg and multiple doses of 3.1 mg QD for 7 days and 4.65 mg BID for 14 days. The wide safety margin is predicted to enable doses capable of durable target engagement in the lung, which are expected to enhance mucociliary clearance in people with cystic fibrosis.