A_{lumen}/A (all $p < 0.001$), but not in A_{wt}/A ($p = 0.35$). Between 64% and 66% of AA pairs were defined as bronchiectasis and 59% as AWT.
Conclusions: Progressive bronchiectasis can be observed in CwCF during late childhood into adolescence. AA analysis results agree with PRAGMA-CF results to monitor disease progression in CwCF.
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Reference

[1] Wijker NE, Vidmar S, Grimwood K, Sly PD, Byrnes CA, Carlin JB, *et al.* Early markers of cystic fibrosis structural lung disease: Follow-up of the ACFBAL cohort. *Eur Respir J* 2020;55(4).

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Effects of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in patients with cystic fibrosis and one or two F508del alleles

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Background: We recently demonstrated that triple combination cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) improves CFTR function in airway and intestinal epithelia to 40% to 50% of normal in patients with CF with one or two F508del alleles. In previous studies, this improvement in CFTR function was shown to improve clinical outcomes, but effects on the lung clearance index (LCI) determined using multiple-breath washout and abnormalities in lung morphology and perfusion detected using magnetic resonance imaging (MRI) have not been studied. The aim of this study was to examine the effect of ELX/TEZ/IVA on LCI and lung MRI scores in people with CF and one or two F508del alleles aged 12 and older.
Methods: This prospective, observational, multicenter, postapproval study assessed LCI and lung MRI scores before and 8 to 16 weeks after initiation of ELX/TEZ/IVA.
Results: Ninety-one people with CF, including 45 heterozygous for F508del and a minimal function mutation (MF) and 46 homozygous for F508del, were enrolled. Treatment with ELX/TEZ/IVA improved LCI in F508del/MF (−2.4, interquartile range (IQR) −3.7 to −1.1; $p < 0.001$) and F508del homozygous (−1.4, IQR −2.4 to −0.4; $p < 0.001$) patients. ELX/TEZ/IVA also improved the MRI global score in F508del/MF (−6.0, IQR −11.0 to −1.3; $p < 0.001$) and F508del homozygous (−6.5, IQR −11.0 to −1.3; $p < 0.001$) patients.
Conclusions: Our data demonstrate that improvement in CFTR function with ELX/TEZ/IVA improves lung ventilation and abnormalities in lung morphology, including airway mucus plugging and wall thickening in adolescents and adults with CF and one or two F508del alleles in a real-world postapproval setting.
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Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for *F508del-CFTR* and a gating or residual function mutation

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Background: The triple combination regimen of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in people with CF aged 12 years and older with cystic fibrosis (CF) and heterozygous for *F508del-CFTR* and either a *CFTR* gating mutation (*F508del*-gating genotypes) or a residual function mutation (*F508del*-residual function genotypes). A 96-week, Phase 3, open-label extension study was conducted to assess long-term safety and efficacy in these participants.
Methods: Participants received ELX 200 mg once daily/TEZ 100 mg once daily/IVA 150 mg every 12 hours. The primary endpoint was safety and tolerability; secondary endpoints included absolute changes in percent predicted FEV_1 ($ppFEV_1$), sweat chloride concentration, body mass index (BMI), body weight, and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score.
Results: 251 participants (*F508del*-gating genotypes, n = 92; *F508del*-residual function genotypes, n = 159) were enrolled and dosed. Mean (SD) exposure to ELX/TEZ/IVA was 89.3 (20.0) weeks. Overall, 241 participants (96.0%) had an adverse event (AE), which for most were mild (32.3%) or moderate (55.0%) in severity. The exposure-adjusted rates of AEs and serious AEs (589.36 and 13.38 events per 100 patient years) were lower than in the 8-week parent study (1033.98 and 26.74 events per 100 patient years). Thirteen patients (5.2%) had AEs that led to treatment discontinuation (increased liver function tests [n = 6], psychiatric events [n = 4], other events [n = 3]), and there was one death due to an operative complication during resection of a cecal mass, which was not considered related to ELX/TEZ/IVA. Following a 4-week run-in period with either IVA or TEZ/IVA, participants who received ELX/TEZ/IVA in the parent study had improvements in $ppFEV_1$, sweat chloride concentration, and CFQ-R respiratory domain score that were maintained to Week 96 of this extension study, while participants who started ELX/TEZ/IVA in the extension study had similar improvements from parent study baseline at Week 96 (Table 1).

Table 1:
Efficacy Results

Endpoints	Control → ELX/TEZ/IVA N=126 → 121	ELX/TEZ/IVA → ELX/TEZ/IVA N=132 → 130
Absolute change in ppFEV$_1$ at Week 96, mean (SD), percentage points	4.1 (0.8)	3.7 (0.8)
Absolute change in SwCl at Week 96, mean (SD), mmol/L	-23.0 (1.4)	-22.6 (1.4)
Absolute change in BMI at Week 96, mean (SD), kg/m^2	1.15 (0.15)	0.83 (0.15)
Absolute change in weight at Week 96, mean (SD), kg	3.6 (0.5)	2.9 (0.5)
Absolute change in CFQ-R respiratory domain score at Week 96, mean (SD), points	7.2 (1.6)	8.1 (1.5)

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire-Revised; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; FEV$_1$ = forced expiratory volume in one second; SwCl = sweat chloride. Results are least-squares mean absolute change (standard deviation) from baseline of the parent study following a 4-week IVA or TEZ/IVA run-in period.

Conclusions: ELX/TEZ/IVA continued to be generally safe and well tolerated in participants aged 12 years and older with *F508del*-gating or *F508del*-residual function genotypes, with no new safety findings. Improvements in lung function, respiratory symptoms, and CFTR function reported in the parent study were maintained through this extension study. These results demonstrate the favorable safety profile and durable clinical benefits of ELX/TEZ/IVA treatment in this population.
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Pilot study of sweat induction using pilocarpine microneedles during sweat test in healthy adults without cystic fibrosis

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Background: The sweat test using pilocarpine iontophoresis remains the gold standard for diagnosing cystic fibrosis (CF), but the need for specialized equipment and training and higher rates of inadequate sweat collection in infants and young children limit access and reliability. These shortcomings can lead to delays in diagnosis and initiation of therapies in children with CF. Response and adherence to CF transmembrane conductance regulator (CFTR) modulators can also be monitored with sweat testing, but limitations of the current method of sweat testing do not permit its use as a point-of-care test.
Methods: We created a simplified method for sweat testing that eliminates the equipment and complexity of iontophoresis by developing a skin patch containing solid microneedles made of pilocarpine. Pressing the patch to the skin is intuitive and painless, and the microneedles rapidly dissolve in the skin to induce sweating, followed by the conventional sweat collection procedure using Macroduct collectors. We conducted a nonrandomized clinical trial in healthy human subjects (clinicaltrials.gov - NCT04732195) with pilocarpine microneedle patches on one forearm and pilocarpine iontophoresis on the other forearm. Sweat volume and sweat chloride concentration were measured in the collected samples from each method. Macroduct collectors were weighed before and after collection of sweat to calculate total sweat output. Subjects were also monitored for any pain or discomfort during testing using a standardized pain score, and skin erythema at the site of application was quantified for each method using a validated erythema assessment scale.
Results: Fifty paired sweat tests were conducted in 16 men and 34 women aged 19 to 61 (22 Caucasian, 12 Asian, 7 African American, 9 Hispanic). There were two participants (both Asian) in whom neither method produced sweat. Total sweat volume collected in the remaining 48 sweat tests was not significantly different for the iontophoresis method (mean 43.8 g, 95% CI, 34.6–53.0 g) and microneedle patch method (mean 41.2 g, 95% CI, 34.1–48.3) ($p = 0.47$). Total mean pilocarpine delivered into the skin from the microneedle patches was 1.09 ± 0.43 mg, which was not significantly different from the 1.18 ± 0.66 mg of pilocarpine delivered using iontophoresis ($p = 0.66$). Overall, participants tolerated the procedures well, with no significant difference in pain or erythema at the site of testing between the microneedle patch method and the iontophoresis method.
Conclusions: The pilocarpine microneedle patch method for sweat testing delivered a similar amount of pilocarpine to the skin as the standard of care pilocarpine iontophoresis method and achieved comparable sweat output. Further studies are being planned in CF subjects to validate this method. Further innovations in the sweat testing technique could allow at-home monitoring and in-clinic point-of-care testing.
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Use of sweat chloride testing to assess adherence to and efficacy of elexacaftor/tezacaftor/ivacaftor treatment in a pediatric cystic fibrosis clinic

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Background: The use of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for patients aged 6 and older with cystic fibrosis (CF) and qualifying mutations has had a tremendous positive impact on lung function and quality of life for many people with CF. Clinical trial data demonstrated substantial increases in forced expiratory volume in 1 second (FEV$_1$), large decreases in sweat chloride values, and decreases in pulmonary exacerbation rates. Our clinic made the decision to use sweat chloride testing to assess real-world physiological responses to ELX/TEZ/IVA at the individual level and discover whether adherence factors affected values [1].
Methods: Our pediatric CF program performed sweat chloride testing on children with CF who had been using ELX/TEZ/IVA for at least 1 month. Pre ELX/TEZ/IVA and best post-ELX/TEZ/IVA lung function (FEV$_1$) were recorded. Pre-ELX/TEZ/IVA spirometry was performed within the month before starting treatment and post-ELX/TEZ/IVA spirometry within 1 month after initiation. The CF pharmacist with the distributing pharmacy reconciled refill history for ELX/TEZ/IVA to assess adherence, in addition to interviews with patients and parents. Twenty-two patients aged 6 to 20 underwent sweat chloride testing. Baseline measurements included mean percentage predicted FEV$_1$ (FEV$_1$pp) of 96.9% (range 63–136%) and mean sweat chloride of 103.7 mmol/L (range 37–122 mmol/L).
Results: The mean increase in FEV$_1$pp after ELX/TEZ/IVA treatment was 18.4 points (range 7–40 points). Mean post-FEV$_1$pp was 115.3% (range 86–156%). Mean decrease in sweat chloride was 61 mmol/L (range 24–89 mmol/L), with mean sweat chloride levels of 42.7 mmol/L (range 13–74 mmol/L). Interesting results were found regarding medication adherence. Two patients who underwent sweat chloride testing had missed their last five doses of ELX/TEZ/IVA because of delivery problems and had modest decreases in sweat chloride. After resuming regular dosing, one patient had a further decrease of 19 mmol/L and the other of 20 mmol/L. Another pediatric participant with a robust post-ELX/TEZ/IVA FEV$_1$pp increase (27 percentage points) experienced a decline in lung function back to pre-ELX/TEZ/IVA levels despite reported good adherence. Sweat chloride was unchanged from pre-ELX/TEZ/IVA levels (96 mmol/L, 97 mmol/L). Further questioning revealed that he had not taken any ELX/TEZ/IVA for several weeks because he was feeling well and was unsupervised. Direct parental and school supervision of ELX/TEZ/IVA administration was instituted, with subsequent increase in FEV$_1$ and decrease in sweat chloride to 40 mmol/L and 42 mmol/L, a decrease of 54 mmol/L.
Conclusions: Sweat chloride testing is a useful tool to determine an individual's response to ELX/TEZ/IVA treatment. In a real-world setting, our results indicate an even greater effect on lung function and sweat chloride