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

than previously reported. Based on our limited experience, sweat chloride testing may be useful to identify potential adherence problems and to emphasize the importance of consistent ELX/TEZ/IVA use to achieve the best outcomes.

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Reference

[1] Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, *et al.* Elexacaftor/tezacaftor/ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019;381:1809–19. https://doi:10.1056/nejmoa1908639

GI/NUTRITION

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Body mass index versus mid-upper arm circumference: Can we replace the gold standard?

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Background: Body mass index (BMI) has long been used as a measure and predictor of health in the general population. For people with cystic fibrosis (PwCF), it has been established as the gold standard for nutrition assessment because optimal BMI correlates with better lung function, measured according to forced expiratory volume in 1 second (FEV_1), although as in the general population, BMI use in PwCF has limitations, because it does not distinguish lean body mass from fat mass [1]. The rise in obesity in PwCF prompted our search for a better predictor of nutritional status in the pediatric CF population [2]. Mid-upper arm circumference (MUAC) is an established measure of pediatric nutrition status and predictor of fat mass [3]. In 2021, our care center began including MUAC measurements as part of our nutrition assessment in children with CF. The objective of this study was to compare BMI and MUAC nutrition assessment methods in children with CF.

Methods: An institutional review board–approved, single-center retrospective analysis was performed on 87 patients with an average age of 10.7 ± 4.2. Data were collected on BMI, MUAC, and FEV_1 from April 2021 to March 2022. Correlation was assessed between BMI Z-scores and MUAC Z-scores, between MUAC Z-scores and FEV_1, and between BMI Z-scores and FEV_1. Subsequent-visit BMI, MUAC, and FEV_1 measurements were obtained in 34 patients.

Results: BMI and MUAC Z-scores had a statistically significant positive linear correlation. MUAC Z-scores identified more patients as malnourished than BMI Z-scores. At the baseline visit, MUAC Z-score identified 12 of 75 children (16%) with CF who were identified as well nourished according to BMI Z-score as having mild or moderate malnutrition (Cohen kappa statistic=0.46, 95% CI, 0.27-0.65). FEV_1 did not differ significantly between those who BMI and MUAC identified as well-nourished and those who only MUAC identified as malnourished. Of the three values (BMI, MUAC, FEV_1), FEV_1 at baseline remained the best predictor of FEV_1 at the subsequent visit.

Conclusions: Based on our review, these results lend support to prior evidence that more patients were identified as malnourished according to MUAC than BMI, but because of the small sample size and retrospective nature of this review, a larger, multicenter study on MUAC as a nutrition assessment method in children with CF is necessary to determine correlation between MUAC and lung function.

References

[1] Soltman S, Hicks RA, Naz Khan F, Kelly A. Body composition in individuals with cystic fibrosis. *J Clin Transl Endocrinol* 2021 30;26:100272. https://doi: 10.1016/j.jcte.2021.100272

[2] Kutney KA, Sandouk Z, Desimone M, Moheet A. Obesity in cystic fibrosis. *J Clin Transl Endocrinol* 2021;26:100276. https://doi: 10.1016/j.jcte.2021.100276

[3] Chomtho S, Fewtrell MS, Jaffe A, Williams JE, Wells JC. Evaluation of arm anthropometry for assessing pediatric body composition: Evidence from healthy and sick children. *Pediatr Res* 2006;59 (6):860–865. https://doi: 10.1203/01.pdr.0000219395.83159.91

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Impact of elexacaftor/tezacaftor/ivacaftor on body composition in a small cohort of youth with cystic fibrosis

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Background: The triple combination cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been shown to be highly effective in improving pulmonary function, increasing body mass index (BMI), and reducing pulmonary exacerbations [1,2]. With increases in BMI and recent reports of obesity in the CF population, closer evaluation of the impact of ELX/TEZ/IVA on body composition may inform metabolic disease risk.

Methods: This was a secondary analysis of a prospective observational study assessing annual, frequently sampled oral glucose tolerance tests (OGTTs) and dual-energy X-ray absorptiometry (DXA) in people with CF aged 6 and older. Inclusion criteria were confirmed diagnosis of CF treated with ELX/TEZ/IVA and available DXA scan results before and after triple combination therapy. Exclusion criteria were use of medications affecting glucose homeostasis, including insulin; pulmonary exacerbations or admissions in the 8 weeks before the study visit; and pregnancy. Paired *t*-tests were used to compare normally distributed variables and Wilcoxon signed rank tests for non-normally distributed variables. Measurements of body composition using DXA included body free fat mass adjusted for height (FFMI) and total body fat mass adjusted for height (FMI). OGTTs with sampling at 0, 10, 30, 60, 90, and 120 minutes for glucose, insulin, and c-peptide were obtained. Integrated area under the curve (iAUC) for each was calculated. Homeostatic model assessment of insulin resistance (HOMA2 IR) was calculated as an estimate of insulin sensitivity. Spirometry data from the most-recent clinic visit were obtained through chart review.

Results: Eight participants (median age 22.1, interquartile range (IQR) 16.2–28.2; 87.5% male were included in the analysis. Mean weight z-score was −0.52 (IQR −1.51 to −0.31), and mean BMI z-score was −0.11 (IQR −0.7–0.87). Median time on ELX/TEZ/IVA was 11 months (IQR 10.8–11.3). All participants were pancreatic insufficient, and 50% were homozygous F508del. Table 1 presents clinical outcomes before and after ELX/TEZ/IVA. Weight increased from 58.6 kg to 68.9 kg ($p = 0.01$), whereas BMI z-score did not change. FMI increased ($p = 0.04$), but FFMI did not change. Glucose iAUC did not change ($p = 0.23$). Insulin secretion measured according to iAUC and C-peptide iAUC increased ($p = 0.02$), and HOMA2 IR, as an index of insulin resistance, increased ($p = 0.01$).

Conclusions: In a small cohort of people with CF treated with ELX/TEZ/IVA for less than 1 year, weight and FMI increased, whereas FFMI did not change. OGTT-derived estimates of insulin secretion (iAUC) and insulin resistance (HOMA2 IR) increased. Larger studies are needed to evaluate the effects of highly effective triple therapy on body composition, particularly body fat distribution, and its association with insulin resistance in subjects with CF.

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