

were measured. LCI was measured using an Exhalizer D MBW device (EcoMedics, Duernten, Switzerland; Spiroware 3.3.1). MBW Xe-MRI was performed as previously described [3], with the ^{129}Xe dose (10% of total lung capacity) was topped with nitrogen to a volume of 1/6th total lung clearance. CoV_{FV} was calculated by comparing the average value of FV in one voxel to that of its nearest neighbors through image kernel convolution and taking the standard deviation over the mean. The Wilcoxon signed-rank test was used to determine significant changes between visits. Correlations between absolute differences in mean FV and CoV_{FV} and LCI were tested with a Spearman correlation.

Results: Xe-MRI (breath = 1), FV, and CoV_{FV} maps for three representative subjects are shown in Figure 1A. The following values are averages from the maps. Median (IQR) CoV_{FV} was significantly ($p = 0.03$) lower at 1 month (median 0.07, interquartile range [IQR] 0.06–0.08) than at baseline (median 0.10, IQR 0.08–0.14). Absolute changes in CoV_{FV} between visits were found to significantly ($p = 0.003$) and highly ($r = 0.96$) correlate with absolute changes in LCI (Figure 1B). Median FV did not change significantly ($p = .16$) between baseline (0.36, IQR 0.33–0.40) and 1 month (0.41, IQR 0.40–0.44) or correlate significantly with LCI ($r = -0.61$, $p = 0.17$).

Conclusions: CoV_{FV} detected improvements in ventilation homogeneity 1 month after ELX/TEZ/IVA treatment. Absolute changes in CoV_{FV} correlated with LCI. The ongoing study will help clarify the relationship between this novel measure and other imaging outcomes in capturing treatment response.

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Toward targeted exhaled breath analysis for young children in cystic fibrosis care to detect bacteria in the lungs

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Background: Children with cystic fibrosis (CF) are prone to bacterial infections, which can be associated with lung function decline. Consequently, detection of bacteria plays an important role in CF care, but culture-dependent diagnosis of such infections is a challenge in children because of limited sample availability and quality. Exhaled breath analysis measuring volatile organic compounds (VOCs) might be a promising noninvasive, culture-independent tool to identify bacteria. Several explorative studies have suggested that VOCs can differentiate

between bacterial species, although these results are not always consistent. The next step for exhaled biomarkers would be to move from discovery studies to hypothesis-driven targeted analysis, an essential step for clinical application. *Staphylococcus aureus* is a common bacteria found in children with CF. We aimed to test the feasibility of targeted exhaled breath analysis in children with CF in a proof-of-concept study for the detection of *S. aureus* using previously identified VOCs and whether this could discriminate between *S. aureus*-positive and -negative cultures.

Methods: Children with CF aged 1 to 6 were included. Exhaled breath samples were stored in thermal desorption tubes and analyzed using gas chromatography–mass spectrometry (GC-MS). Microbiological cultures were collected on the same day. After a literature review to identify *S. aureus*-related VOCs, targeted peak detection using AMDIS (v.2.68) was performed on the GC-MS dataset, and the resulting peak intensities were used for multivariate modeling using sparse partial least squares discriminant analysis (sPLS-DA), after which the predicted outcomes (*S. aureus* positive or negative) were compared with the actual microbiological outcomes. Statistical analyses were performed in R-Studio (v.1.3).

Results: Exhaled breath collection was attempted in 24 children with CF, and was successful in 83% ($n = 20$, median age 4, interquartile range 2–6). Of nine patients who had a positive culture for *S. aureus*, six were taken by a nasopharyngeal swab, two from sputum, and one from bronchoalveolar lavage fluid. Two patients had a positive culture for *Haemophilus influenzae* and one for *Moraxella catarrhalis*. Eight patients had a negative culture. We identified five VOCs associated with *S. aureus* from the literature review (≥ 2 consistent notations), which were used to predict culture positivity for *S. aureus*, resulting in accuracy of 70%, specificity of 89%, and sensitivity of 55%. The positive predictive value of the test was 86%, and the negative predictive value was 62%.

Conclusions: Targeted analysis of MS-driven exhaled VOC profiles appears to enable detection of pathogens in exhaled breath. We showed that noninvasive breath collection for targeted exhaled breath analysis is feasible in young children and that VOCs associated with *S. aureus* were detectable. One of the limitations of this study is the small sample size and that most microbiology cultures were taken using a nasopharyngeal swab, which may explain the low sensitivity of the model. More research should be done to evaluate this promising methodology in larger cohorts, preferably using more-sensitive microbiological sampling methods.

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Inflammation-based scoring systems and ratios to identify people with cystic fibrosis at risk for intravenous antibiotic therapy

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Background: Pulmonary disease in cystic fibrosis (CF) is characterized by chronic bacterial infection with recurrent pulmonary exacerbations (PEX), which are associated with high systemic inflammatory marker levels. Because PEX are associated with higher morbidity and mortality, prevention is an important therapeutic goal in the treatment of people with CF (PwCF). Identifying patients at risk for future PEX can be challenging in clinical practice. The objective of this study was to compare established and novel markers of chronic inflammation and their ability to predict the need for intravenous antibiotic therapy (nIVT) as a surrogate marker for PEX or decline in pulmonary status in PwCF.

Methods: Individuals aged 18 and older treated between 2014 and 2018 in the adult CF center of the university hospital Munich, Germany, who had at least two pulmonary function tests per year for a 3-year period were included in this retrospective, longitudinal study. Baseline was defined as the first year after the first measurement. The follow-up period was time between baseline and end of follow-up. Neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, C-reactive protein (CRP)/albumin ratio, Glasgow prognostic score, and CF-Able score of patients with and without nIVT during follow-up were compared. In the univariate analysis, we used chi-square and Fisher exact tests to compare categorical scores and t-tests to compare numerical scores. In the multivariate analysis, we used

logistic regression models adjusted for age, sex, nIVT at baseline, body mass index, homozygote *delF508* mutation, diabetes mellitus, chronic pulmonary infection (*Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Mycobacterium abscessus*, *Achromobacter xylosoxidans*), and use of a CF transmembrane conductance regulator modulator therapy. Model Akaike information criteria were compared to identify the marker with the best prediction ability. Results are reported as odds ratios with *p*-values.

Results: Of 131 PwCF (43.5% female, mean age 34.0) evaluated, 75 (57.3%) had at least one nIVT during follow-up. In the univariate analysis, having an nIVT during follow-up was significantly associated with higher inflammation scores for all markers examined. In the multivariate analysis, the following markers at baseline were significantly associated with having an nIVT during follow-up: CRP (OR = 7.29, *p* = 0.01), CRP/albumin (OR = 1.09, *p* = 0.004), low lymphocyte/monocyte ratio (OR = 0.55, *p* = 0.03), high neutrophil/lymphocyte ratio (OR = 1.51, *p* = 0.01), Glasgow prognostic score of 1 vs. 0 (OR = 3.52, *p* = 0.02), and CF-Able score of 2 to 4.5 vs. less than 2 (OR = 3.82, *p* = 0.02). Comparison of the regression models showed that CRP/albumin ratio was superior to the other models examined in differentiating patients with and without nIVT during follow-up.

Conclusions: Our retrospective study found that several inflammation-based scoring systems or ratios established for other disease entities can identify patients with nIVT in PwCF. Although the CF-Able score was not designed to predict PEx, it includes some variables associated with greater risk for PEx and, correspondingly, nIVT. The easily calculated CRP/albumin ratio is superior to CF-Able score in distinguishing PwCF with nIVT from those without and thus represents an interesting possibility for clinical use.

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First-in-human study to evaluate safety, tolerability, and pharmacokinetics of GDC-6988 (ETD002), a selective inhaled potentiator of the TMEM16A chloride channel

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Background: It is thought that therapies that restore fluid transport at the airway surface improve mucus clearance and reduce frequency of pulmonary exacerbations. Although effective, cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator therapies are not currently indicated for approximately 10% of people with CF and do not fully relieve the disease even in those for whom they are indicated. As such, there is an important need for novel approaches to address patients unsuitable for current CFTR modulator therapies and those who do not respond optimally. GDC-6988 is a potent, selective potentiator of TMEM16A and is expected to enhance the opening of the chloride channel in response to high intracellular calcium levels, increase airway fluid secretion, and promote mucus hydration and clearance.

Methods: Study ET-TMEM-01 was a first-in-human, randomized, double-blind, placebo-controlled interventional study to assess the safety, tolerability, and pharmacokinetics of single and multiple ascending doses of inhaled nebulized GDC-6988 (ETD002) in healthy volunteers (NCT04488705). The study consisted of three parts. Part A evaluated single doses of GDC-6988 up to 150 mg, and Part B evaluated GDC-6988 up to 75 mg twice per day (BID) for up to 14 days. Part C was added after study initiation to explore the effect of pretreatment with albuterol on changes in lung function observed during Part B and consisted of albuterol pretreatment on Days 5 to 7 of a 7-day treatment period with 75 mg of GDC-6988 BID.

Results: Seventy-six subjects received GDC-6988 or placebo (Part A = 36; Part B = 18; Part C = 8). All adverse events were mild or moderate in severity. Adverse events reported in more than 10% of subjects included headache (6 [12.5%] subjects in Part A, 4 [16.7%] subjects in Part B, none in Part C). In Part B, decreases in forced expiratory volume in 1 second (FEV₁) of at least 10% from baseline to 30 minutes after at least one dose were seen in some subjects who received GDC-6988 (1 subject at 22.5 mg BID, 3 subjects at 45 mg BID, 4 subjects at 75 mg BID), which generally resolved by the next predose measurement. Of these, two subjects receiving 75 mg GDC-6988 BID withdrew from study treatment because of an adverse event: one of

moderate chest discomfort and the other of predefined lung function stopping criteria. The adverse events were associated with transient decreases in FEV₁ of up to 17% and 21.7%, respectively, that completely or mostly resolved within 4 hours. There was no apparent correlation between systemic exposure and change in FEV₁. In Part C, FEV₁ variations were again observed on Days 1 to 4, although 200 µg of albuterol pretreatment on study Days 5 to 7 mitigated the FEV₁ decreases seen in Part B of the study (Figure 1). Key pharmacokinetic parameters of GDC-6988 maximum serum concentration (C_{max}) and area under the curve (AUC) increased with increasing doses, with relatively high variability (coefficient of variation of ~80% in AUC and C_{max}). C_{max} and AUC were approximately dose proportional in the single-ascending-dose cohorts. No clear accumulation was observed in multiple-ascending-dose cohorts because of the relatively short elimination half-life. Co-administration of GDC-6988 with albuterol had little impact on GDC-6988 pharmacokinetic parameters, but variability in the exposure-related parameters was reduced.

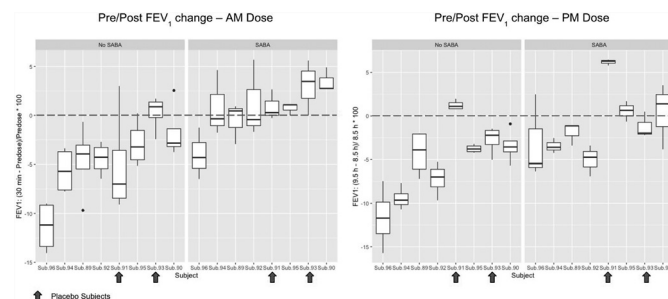


Figure 1. Percentage change from baseline in forced expiratory volume in 1 second 30 minutes after administration of GDC-6988

Conclusions: GDC-6988 is generally safe and well tolerated at doses of up to 75 mg BID by nebulized inhalation. Reductions in FEV₁ are self-limited and can be mitigated with pretreatment albuterol. As expected, systemic exposure levels of GDC-6988 are low. A Phase 1B study of GDC-6988 in healthy volunteers with a dry powder inhaler formulation is planned.

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Estimating personalized lung function trends from routine clinical care to facilitate analysis of daily data capture using remote technologies

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Background: Automated data capture through remote monitoring using apps and wearable devices has enabled researchers to capture daily biometric data, allowing for investigation of personalized trends and novel predictors of clinical outcomes. An example is the remote capture of physical activity levels using Fitbit activity trackers, but it is challenging to interpret associations between daily predictors and outcomes that are measured infrequently, for example forced expiratory volume in 1 second (FEV₁), which is typically measured quarterly at clinical encounters and therefore may not match with data collected from daily remote monitoring. As a result, daily data must be collapsed into a small number of categories to match with the time points of FEV₁ measurements, ignoring the granular detail. The aim of this study was to investigate optimal parameters for using flexible polynomial regression to estimate personalized trends in FEV₁ over time in children and adolescents with cystic fibrosis (CF) to facilitate detailed analysis of frequently collected novel outcomes.