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 (FEV_1) 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 FEV_1 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 FEV_1. In Part C, FEV_1 variations were again observed on Days 1 to 4, although 200 µg of albuterol pretreatment on study Days 5 to 7 mitigated the FEV_1 decreases seen in Part B of the study (Figure 1). Key pharmacokinetic parameters of GDC-6988 maximum serum concentration (Cmax) and area under the curve (AUC) increased with increasing doses, with relatively high variability (coefficient of variation of ~80% in AUC and Cmax). Cmax 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.

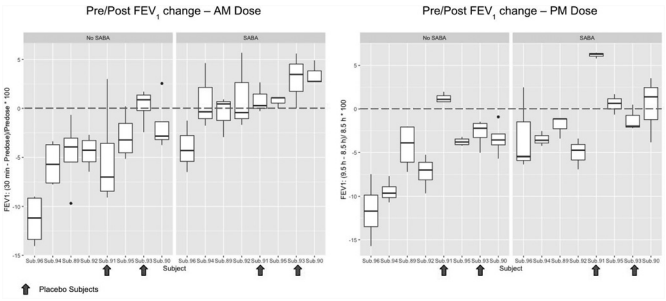

Figure 1. Percentage change from baseline in forced expiratory volume in 1 second 30 minutes after administration of GDC-6988

Conclusions: GDC-6988 is generally safe and well tolerated at doses of up to 75 mg BID by nebulized inhalation. Reductions in FEV_1 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 (FEV_1), 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 FEV_1 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 FEV_1 over time in children and adolescents with cystic fibrosis (CF) to facilitate detailed analysis of frequently collected novel outcomes.