Table 1 (abstract 173):
Changes in lung clearance index (LCI), percentage predicted forced expiratory volume in 1 second (ppFEV$_1$), sweat chloride (SwCl), and the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) from baseline to 1 month after initiation of elexacaftor/tezacaftor/ivacaftor

Outcome	Visit	n	Mean ± SD	Change (95% CI)
LCI(2.5)	Baseline, pre-ETI	94	7.25 ± 1.27	
	1 month post-ETI	96	6.55 ± 0.74	-0.82 (-1.10, -0.54)
ppFEV1	Baseline, pre-ETI	124	99.9 ± 14.1	
	1 month post-ETI	118	104.8 ± 13.9	+4.97 (3.04, 6.90)
SwCl	Baseline, pre-ETI	102	87.0 ± 25.6	
	1 month post-ETI	99	42.3 ± 16.5	-44.9 (-48.4, -41.3)
CFQ-R	Baseline, pre-ETI	124	86.3 ± 10.4	
	1 month post-ETI	117	89.9 ± 10.9	+3.76 (1.70, 5.82)

(CFQ-R) respiratory domain score. Changes from baseline to 1-month follow-up were analyzed using a paired t-test on a complete-case cohort.
Results: Of 125 participants at 20 sites enrolled in the Pediatric Substudy, 119 had completed the 1-month visit at the time of analysis. Mean age at initiation of ELX/TEZ/IVA was 9.2 ± 1.8 years, and 44% were female at birth. There were 65 (52%) F508del homozygous participants, 34 (27%) F508del heterozygous participants with a minimal-function second allele, and 26 (21%) participants with other CFTR variants (heterozygotes with gating or residual function second alleles or no F508del alleles). Results at baseline and 1 month and change (mean, 95% CI) are reported in Table 1. LCI, FEV$_1$pp, sweat chloride, and CFQ-R respiratory domain score all improved significantly from baseline to the 1-month visit.
Conclusions: In this ongoing, prospective, observational postapproval study of ELX/TEZ/IVA in children, preliminary results at 1-month follow-up indicate significant improvements in LCI, FEV$_1$pp, sweat chloride, and self-reported respiratory symptoms. At this interim analysis, the magnitude of change for all outcome measures was lower than reported in the Phase 3 clinical trials in this age range, although baseline lung function was better in the current study—similar to what has been observed for the PROMISE study in subjects aged 12 and older [1]. Future reports will evaluate a broader range of endpoints for up to 4 years.
Acknowledgements: Funded by the Cystic Fibrosis Foundation.

Reference

[1] Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, *et al.*; PROMISE Study group. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: A clinical trial. *Am J Respir Crit Care Med* 2022;205(5):529–539. https://doi:10.1164/rccm.202108-1986OC.

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Identification of physiological characteristics at baseline and 1 and 6 months that segregate lung function response to ivacaftor using proteomic analysis

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Background: Ivacaftor targets abnormal gating of the cystic fibrosis (CF) transmembrane conductance regulator (CFTR). The G551D Observational (GOAL) study is a longitudinal observational cohort of patients with at least one G551D mutation starting ivacaftor. Six months after drug initiation, there was a mean change in percentage predicted force expiratory volume in 1 second (FEV$_1$pp) of 6.7% (95% CI, 4.9–8.5%) and a mean decline in sweat chloride of 54 mEq (95% CI, −57.7 to −49.9 mEq), although approximately half of study participants who exhibited physiologic CFTR modulation (sweat chloride change of −80 to −60 mEq/L) did not have improvement in FEV$_1$. The aim of this study was to understand the biological basis for lack of lung function response to modulator therapy.
Methods: Plasma samples were obtained from GOAL study participants with baseline FEV$_1$pp of 64% to 84% and sweat chloride change at 6 months of −80 mEq/L to −60 mEq/L. Samples were blinded, randomized, albumin depleted, fractionated, and subjected to mass spectrometry proteomics. Samples from lung function responders, with an increase in FEV$_1$pp of 5% or more at 1 and 6 months (baseline n = 15, 1 month n = 15, 6 months n = 14), were compared with those of nonresponders, with change in FEV$_1$pp of less than 5% at 1 and 6 months (baseline n = 27, 1 month n = 15, 6 months n = 15).
Results: At baseline, using standard stringency filters on the data, we identified 2,820 protein isoform differences between lung function nonresponders and responders. Pathway analysis of these proteins identified enrichment for wound healing ($p < 0.001$), cellular organization ($p < 0.001$), and cell migration ($p < 0.001$) (Figure 1). One month after ivacaftor initiation, there were 1,267 protein differences that continue to be associated with cellular organization ($p < 0.001$) and new associations with regulation of smooth muscle contraction ($p < 0.001$), catecholamines ($p = <0.001$), and nitrogen compound metabolic process ($p < 0.001$). Six months after ivacaftor initiation, there were 1,757 protein isoform differences that continued to be associated with cellular organization ($p < 0.001$) and migration ($p = 0.001$). High-stringency filtering of the data identified alterations in ciliary movement ($p < 0.001$), inflammation ($p < 0.001$), and remodeling ($p < 0.001$) as segregators of 6-month response at baseline. At 1 month, application of high-stringency filters to the data identified differences in interleukin-18-mediated signaling ($p = 0.001$). At 6 months, the high-stringency filters identified inflammation ($p < 0.001$), positive regulation of nitrogen compound metabolic process ($p < 0.001$), and negative regulation of nitrogen compound metabolic process ($p < 0.001$).

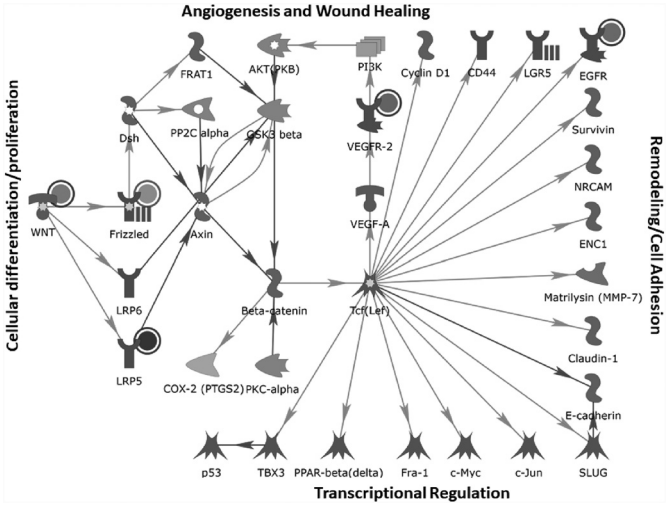

Figure 1. Pathway analysis comparing plasma protein expression before ivacaftor initiation of lung function nonresponders and responders. MetaCoreby Clarivate, version 21.3 build 70400, pathway analysis software was used to analyze protein expression differences in individuals with cystic fibrosis (CF) before initiation of CF transmembrane conductance regulator modulation therapy using a standard stringent cutoff. Lung function responders had an increase in percentage predicted forced expiratory volume in 1 second of more than 5% 6 months after drug initiation. These analyses revealed wound healing, proliferation, and structural remodeling.

Conclusions: Before initiation of ivacaftor, there are protein differences between patients with lung function response sustained at 6 months and those without a change in lung function at 6 months. Pathway analysis reveals that these differences are associated with wound healing and cell migration, suggesting that differences in structural remodeling and inflammation before therapy initiation may affect lung function response and diminish the full benefit of therapy. By 6 months, pathway differences in nitrogenous compound metabolic processes suggest that differences in the processing of ivacaftor, an aromatic nitrogen-containing compound, may decrease the benefit of high-efficacy modulation of CFTR.

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QuestionCF 2022: Updating the top 10 research priorities for clinical research in cystic fibrosis

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Background: The top 10 research priorities for clinical research in cystic fibrosis (CF) were identified in 2017 through a James Lind Alliance Priority-Setting Partnership, engaging the patient and clinical communities [1]. Funders have adopted these priorities, leading to at least £23 million of funding in the United Kingdom alone. Much has changed in CF over the past 5 years, so we are undertaking a global update to identify priorities in post-modulator times.

Methods: Led by a multinational steering group representative of the patient and clinical communities, we have developed a new methodology. An initial questionnaire administered in January and February 2022 identified which of the 2017 priorities were still relevant and identified new questions to add. The questionnaire was available online in several languages and was promoted through our "QuestionCF" social media channels, plus professional, charity, and patient group partners. The new suggestions were checked and grouped, and umbrella questions were formed where possible. A second ranking survey administered in May and June 2022 asked individuals to select their personal top 10, and an online workshop involving representatives of the patient and clinical communities will agree on the updated top 10 priorities in summer 2022.

Results: We had 1,608 responses to the first survey from 1,370 individual respondents. Of these, 74% were from lay people (people with CF and their families and friends) and 26% from health care professionals and researchers in CF. The median age of people with CF answering (or with answers on their behalf) was 27 (range 0–79). Sixty-five percent of respondents with CF were on modulator therapies, with 14% not yet eligible. We had responses from 29 countries, including North America, Europe, New Zealand, Australia, Africa, and the Middle East. We had 971 question suggestions. We will present the results of the next stage and final updated top 10 priorities for clinical research in CF at the North American Cystic Fibrosis Conference.

Conclusions: Ours is the first James Lind Alliance Priority-Setting Partnership in any medical or disease condition are to update its priorities. We are working with the global community to keep CF research relevant and focused on the needs of people with CF.

Acknowledgements: This work was supported by the Cystic Fibrosis Trust and a Research England, Participatory Research grant.

Reference

[1] Rowbotham NJ, Smith S, Leighton PA, Rayner OC, Gathercole K, Elliott ZC, *et al.* The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and health care providers. *Thorax* 2018;73:388–90. http://dx.doi.org/10.1136/thoraxjnl-2017-210473

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How frequently should the lung clearance index be measured in children with cystic fibrosis?

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Background: The lung clearance index (LCI) can identify individuals with cystic fibrosis (CF) at risk of subsequent lung function decline [1]. Some CF centers have implemented LCI measurements as part of a routine annual assessment, but it is unclear what the optimal monitoring frequency is and whether more-frequent LCI measurements (e.g., every 3 or 6 months) would increase detection of otherwise clinically stable individuals with deteriorating lung function.

Methods: In a prospective longitudinal study, 98 school-aged children with CF were followed, and LCI was measured every 3 months for 2 years. Study visits were categorized as clinically stable (respiratory symptoms judged to be representative of a participant's baseline) or as acute respiratory event visits (increased respiratory symptoms). The baseline LCI for each study visit to calculate a relative change was defined as an LCI measurement from a stable visit 3, 6, or 12 months before. A significant change was defined as an LCI increase of 10%, a threshold than can identify clinically meaningful changes in LCI [2]. We used generalized estimating equation models for linear outcomes to determine whether different testing intervals affected the magnitude of LCI change between stable visits and binary outcomes to determine the proportion of visits associated with a 10% or greater worsening in LCI.

Results: On average, LCI changes between stable visits were similar when a 3- (0.22%, 95% CI, −1.2–1.6%; reference group), 6- (0.45%, 95% CI, −0.1–2.0%; $p = 0.85$), or 12-month (1.44%, 95% CI, −0.13–3.0%; $p = 0.33$) baseline was used to calculate changes. On an individual level, a similar proportion of stable visits were associated with a 10% or greater increase in LCI when different baseline LCI values were used to calculate changes (3-month