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### A qualitative needs assessment of people with cystic fibrosis and research coordinators to inform future clinical trials incorporating home spirometry as an endpoint

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**Background:** Home spirometry holds promise as a primary endpoint for clinical trials. Qualitative needs assessments describing the practices and perspectives of people with cystic fibrosis (PwCF), caregivers of PwCF, and research coordinators (RCs) regarding home spirometry can inform strategies for incorporating home spirometry into clinical trials.
**Methods:** We conducted a series of focus groups that engaged PwCF, caregivers, or RCs (separately), led by an experienced facilitator and conducted via videoconference. PwCF aged 14 and older and caregivers with experience performing home spirometry were recruited through the Cystic Fibrosis Foundation (CFF) Community Voice. RCs with experience coaching home spirometry were recruited through the CFF Therapeutics Development Network from sites participating in the PROMISE study. Participants provided informed consent and completed an online survey before the focus group to describe their demographic characteristics and home spirometry devices. Focus groups elicited current experiences and barriers to and facilitators of home spirometry across six target areas, followed by discussion and prioritization. Target areas for PwCF and caregivers included research incentives, burden of procedures, reminders, remote coaching, training, and spirometry results. Target areas for RCs included participant and RC training, remote coaching, monitoring progress, participant engagement, and institution-specific issues. Qualitative analyses followed the deductive approach of template analysis [1]. Common themes identified in each session were reviewed in all PwCF or RC sessions to identify areas of consensus, which were used to formulate recommendations for future clinical trials.
**Results:** From September to November 2021, 27 PwCF and six caregivers stratified according to age and role (teens, adults aged 18–39, adults aged ≥40, caregivers) participated in seven sessions, and 24 RCs participated in five sessions. Groups identified barriers to and facilitators of use of home spirometry. Although most PwCF and caregivers found home spirometry convenient, many experienced technical barriers, reported a learning curve to home measurement, and expressed uncertainty about the quality and reliability of measurements. Major barriers that RCs identified involved tailoring participant training to individual needs, scheduling remote coaching, and performing effective coaching remotely. Participants offered age-specific recommendations in key domains: training materials and procedures ( for PwCF and RCs), remote coaching, monitoring progress, maintaining engagement, and other areas, including differences in the conduct and interpretation of research versus clinical and home versus office spirometry.
**Conclusions:** Recommendations from this qualitative needs assessment of PwCF, caregivers, and RCs regarding home spirometry in the research setting have been incorporated into the design of OUTREACH, a CFF-funded, multicenter, prospective study of the accuracy, variability, feasibility, and acceptability of home spirometry as a clinical trial endpoint. Our results can also help inform the design of future remote clinical trials.
**Acknowledgements:** This work was supported by CFF ROSENF21A0. We thank all the focus group participants.

### Reference

[1] Crabtree A. A template approach to text analysis: Developing and using code-books. *Doing Qualitative Research* 1992;3:93–109.

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### Chest computed tomography assessment to monitor cystic fibrosis structural lung disease progression in bronchiectasis during late childhood and adolescence

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**Background:** Cystic fibrosis (CF) lung disease is characterized by progressive bronchiectasis and airway wall thickening (AWT) starting in early childhood. Using the Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF), the follow-up of the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study (CF-FAB study) showed that the extent of lung disease in young children with CF (CwCF) was an important risk factor for progressive structural lung disease in adolescence [1]. Recently, a fully automated method was developed and validated to measure airway and artery (AA) dimensions for sensitive detection of bronchiectasis and AWT. The aim of our study was to monitor progression of bronchiectasis and AWT over late childhood into adolescence in a longitudinal follow-up study (CF-FAB) of the ACFBAL cohort using the AA method and PRAGMA-CF.
**Methods:** CF-FAB enrolled CwCF who completed the ACFBAL study in Australia and New Zealand. Computed tomography (CT) scans were obtained at two time points approximately 18 months apart. CT scans were analyzed using manual PRAGMA-CF and the automated AA method (LungQ-AA, v2.1.0, Thirona, the Netherlands). PRAGMA-CF computes the volume fraction of the following structural lung components on the inspiratory CT scan: % bronchiectasis, mucus plugging (%MP), %AWT, and atelectasis (%Atelec). The composite score %Disease (%Dis) is defined as the sum of % bronchiectasis, %MP, and %AWT. LungQ-AA automatically segments the bronchial tree and identifies segmental ($G_0$) and distal ($G_{1\text{-}13}$) airway generation. For each identified airway, the following dimensions are quantified: diameters of airway outer edge ($A_{out}$), airway lumen wall ($A_{lumen}$), artery (A) and airway wall thickness ($A_{wt}$), and AA-ratios: $A_{out}$/A, $A_{lumen}$/A, and $A_{wt}$/A. Bronchiectasis was defined as $A_{out}$/A greater than 1.1 or $A_{lumen}$/A greater than 0.8 and AWT as $A_{wt}$/A greater than 0.3. Mixed-effects models were used for analysis.
**Results:** One hundred twenty CwCF with a mean baseline age of 12.8 ± 1.6 were enrolled, and 115 baseline and 110 follow-up CT scans were obtained with a mean interval of 26 months. Coded CT scans were manually scored in random order using PRAGMA-CF. %Dis increased by 0.44% per year ($p = 0.03$) and % bronchiectasis increased by 0.38% per year ($p = 0.01$), respectively. No significant progression was observed for %AWT ($p = 0.98$). One hundred eighty-five CT scans from 100 CwCF could be analyzed using LungQ-AA (39 excluded because slice thickness was greater than 1.5 mm and 1 for reason unknown). On baseline CT scans (n = 96), 30,792 AA pairs and on follow-up CT scans (n = 89) 32,024 AA pairs were detected from $G_1$ to $G_{13}$ and analyzed; significant progressions were found in $A_{out}$/A and

$A_{lumen}/A$ (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.
**Acknowledgements:** On behalf of the ACFBAL and CF-FAB study groups. This study was supported by grants from the Australian National Health and Medical Research Council (9937868, 351541, 1044829). C.E. Wainwright was supported through Practitioner Fellowship through the Children's Hospital Foundation Brisbane (RG0692016).

## 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.
**Acknowledgements:** This study was supported by an independent medical grant from Vertex Pharmaceuticals Incorporated (IIS-2018-107555), the German Center for Lung Research funded by the German Federal Ministry of Education and Research (82DZL009B1, 82DZL002A1, 82DZL005B1, 82DZL004B1), and the German Research Foundation (CRC 1449–431232613 Z02). The funders had no role in design, management, data collection, analyses, or interpretation of the data or in the writing of the abstract or the decision to submit to the North American Cystic Fibrosis Conference. S.T.P. is a member of the Else-Kröner Forschungskolleg TITUS. S.Y.G. and M.S. are participants of the BIH-Charité Clinician Scientist Program funded by the Charité-Universitätsmedizin Berlin and the BIH.

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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).