WS3.1 The effect of ivacaftor on the rate of lung function decline in CF patients with a *G551D-CFTR* mutation

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Background and Objective: Progressive loss of lung function is a major cause of morbidity in CF patients; more rapid declines are associated with earlier mortality. Ivacaftor improves lung function in CF patients with a *G551D* mutation, but whether treatment affects FEV_1 rate of decline is unknown. Our goal is to examine whether ivacaftor therapy alters the rate of lung function decline in CF patients with a *G551D* mutation compared with CF patients who have *F508del* mutations.
Methods: A propensity score will be used to match CF patients with a *G551D* mutation who received ivacaftor in clinical trials for up to 144 weeks (n = 192) in a 1:5 ratio with patients in the U.S. Cystic Fibrosis Foundation Patient Registry homozygous for the *F508del* mutation. Matching will be based on measures such as age, gender, % predicted FEV_1, and *P. aeruginosa* infection. Inclusion criteria for controls will be *F508del* homozygous genotype, age ⩾6 years, sweat chloride >40 mmol/L, no evidence of lung transplant, and clinical stability based on care episode, medication, and spirometry data. The annual rate of change in % predicted FEV_1 by group will be estimated for up to 3 years and the difference in rate of change between groups will be assessed (mixed effects model).
Results: Preliminary results showed that the annualized rate of decline in % predicted FEV_1 in ivacaftor-treated patients is 0.60 percentage points (95% CI: −1.12, −0.08). The rate of decline in the *F508del* population will be available at the time of this presentation.
Conclusions: This analysis is expected to determine whether ivacaftor therapy alters the rate of decline in FEV_1 for CF patients with the *G551D* mutation.

WS3.2 The effect of ivacaftor treatment on lung ventilation defects, as measured by hyperpolarized helium-3 MRI, on patients with cystic fibrosis and a *G551D-CFTR* mutation

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Objectives: To evaluate the effect of short-term (4 weeks) and long-term (48 weeks) ivacaftor treatment on hyperpolarized helium-3 magnetic resonance imaging (^{3}He-MRI)-defined ventilation defects in patients with cystic fibrosis (CF) and a *G551D-CFTR* mutation on at least 1 allele.
Methods: This was a single-center, 2-part, Phase 2 study of CF patients who had a *G551D-CFTR* mutation and % predicted FEV_1 ⩾40%. Part A was a single-blind, placebo-controlled study comprising 4 weeks of ivacaftor treatment and Part B was an open-label, 48-week study (washout between A and B ⩾4 weeks). Outcome measures were the mean change from baseline in total ventilation defect (TVD, the proportion of total ventilation defect volume to total lung volume) and total defect volume (TDV) at 4 weeks (Part A) and through 48 weeks (Part B), as measured by ^{3}He-MRI.
Results: In Part A (n = 8, mean age 18.9 years), ^{3}He-MRI revealed that ivacaftor treatment reduced the TVD by a mean of 8.2 percentage points ($P = 0.0547$) and the mean TDV by 0.48 L ($P = 0.0313$). In Part B (n = 9, mean age 24.4 years), through 48 weeks the mean decrease in TVD was 6.3 percentage points ($P = 0.1953$) and the mean decrease in TDV was 0.31 L ($P = 0.2656$). These results were associated with a 12.8-point increase ($P = 0.0078$) in mean % predicted FEV_1 in Part A (4 weeks) and a 5.2-point increase in Part B ($P = 0.1953$).
Conclusions: Total ventilation defect volume in patients with CF and the *G551D-CFTR* mutation was responsive to ivacaftor therapy. ^{3}He-MRI may be useful for assessing ventilation defects that may not be captured using traditional spirometry, such as location of defects or disease burden.

WS3.3 MRI-based pulmonary blood flow and lung function in CF patients − flow changes with pulmonary decline

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Objectives: In the current study, we examined relationships between pulmonary bloodflow (PBF) and FEV1 in CF patients with mild vs moderate and severe disease.
Methods: 16 patients with CF were prospectively evaluated. 8 patients were included in the mild CF lung disease group (FEV1 >80% predicted, mean FEV1% = 103.6±10.4; mean age = 14.8±2 yrs, 6 males, 2 females) and 8 were included in the moderate-severe CF lung disease group (FEV1 <80% predicted, mean FEV1% = 56.6±11.6; mean age = 18.0±0.8 yrs, 3 males, 5 females). 17 non-CF, normal subjects served as controls (mean age = 18.6±6.9 yrs; 7 males, 10 females). Aorto-pulmonary collateral blood flow (APCBF) was calculated for each subject. The relationship between APCBF and FEV1% was modeled using nonparametric regression. Group differences were assessed by ANOVA.
Results: APCBF was similar to that of non-CF controls for CF patients with FEV1 >100%. APCBF increased as FEV1% in CF subjects fell below 101.5%, with high APCBF seen in moderate-severe lung disease compared to controls (0.89 vs. 0.20 L/min, $p < 0.0001$). APCBF correlated negatively with FEV1% ($R2 = 0.55$, $p = 0.039$).
Conclusion: APCBF was within the normal range in CF subjects with mild lung disease but rapidly increased as FEV1% dropped below 100%. A significant increase in the APCBF compared to controls was measured in patients with moderate-severe CF lung disease. APCBF may serve as a novel biomarker of early CF pulmonary disease.

WS3.4 Lack of correlation between sputum *Pseudomonas aeruginosa* density and FEV_1 changes among CF patients treated with inhaled antibiotics

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Objectives: We examined changes in sputum *Pseudomonas aeruginosa* (*Pa*) density (log_{10}CFU/g) and FEV_1% predicted among patients (pts) enrolled in a 24 wk randomized comparison of APT-1026 (levofloxacin nebuliser solution; LNS) and tobramycin nebuliser solution (TNS) to determine if there was a relationship between change in bacterial density and FEV_1 (NCT01270347).
Methods: Bivariate linear regressions for FEV_1% predicted change as a function of sputum *Pa* density change were performed at the ends of each of four 28-day study windows (wks 0–4, 4–8, 16–20, 20–24) in pts who had received no antibiotic (ABX) treatments other than one of the study drugs. Relationships between sputum *Pa* density change and FEV_1 change were analyzed using repeated measures models with effects/covariates for treatment, visit, baseline sputum *Pa* density, interaction terms, and relevant baseline characteristics.
Results: 207 pts (143 treated with LNS; 64 with TNS) had data for at least two consecutive visits (i.e. one window); 154 had ⩾2 windows, 85 had ⩾3 windows, and 68 had 4 windows. No significant correlations were observed between 28-day *Pa* sputum density change and FEV_1 change in any study window (P values range: 0.3–0.6; R^2: 0.0015–0.0159) or by treatment group. Repeated measures results were consistent with bivariate regression.
Conclusion: Inhaled ABX presumably provide an FEV_1 benefit via antimicrobial activity. However, individual FEV_1 changes in pts receiving (or being withdrawn from) inhaled ABX for 28 days do not correlate linearly with changes in *Pa* density from expectorated sputum, suggesting that sputum *Pa* density changes inadequately reflect inhaled ABX activity in the CF airway.