228. Cystic fibrosis (adults and children): new therapies and detection of early lung disease

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Effects of the CFTR potentiator, ivacaftor, in two phase 3 trials in subjects with CF who have the *G551D-CFTR* mutation

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Rationale: Two Phase 3 studies were conducted to assess the effect of ivacaftor in subjects with CF who have the *G551D-CFTR* mutation.
Methods: These were randomized, double-blind, placebo-controlled, multicenter studies. Subjects received placebo or ivacaftor (150 mg q12h) for 48 weeks in addition to their prescribed therapies. STRIVE enrolled 161 subjects with CF who were ≥12 years and had % predicted FEV_1 at screening of 40%-90%. ENVISION enrolled 52 subjects who were 6-11 years and had % predicted FEV_1 at screening of 40%-105%.
Results: Analysis of the primary endpoint (absolute change in % predicted FEV_1 through Week 24) showed a significant treatment effect in both studies. The treatment difference was 10.6 percentage points in STRIVE ($P<0.0001$) and 12.5 percentage points in ENVISION ($P<0.0001$) when compared to placebo. In both studies, the improvements were rapid in onset. In STRIVE, there was a 55% reduction in pulmonary exacerbation risk for subjects in the ivacaftor group vs. subjects in the placebo group through Week 48 (P=0.0012). In ENVISION, too few subjects experienced pulmonary exacerbations to make meaningful comparisons. In both studies, most adverse events were respiratory in nature and similar to placebo. In STRIVE, 10 placebo (12.8%) and 6 ivacaftor (7.2%) subjects discontinued treatment. In ENVISION, 4 placebo (15.4%) subjects discontinued treatment while no ivacaftor-treated subjects discontinued.
Conclusions: In subjects with CF 6 years and older with the G551D mutation, ivacaftor was highly effective in the treatment of CF, as evidenced by improvement in clinical outcomes. Safety of ivacaftor was comparable to placebo.
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Effect of ivacaftor on lung clearance index and FEV_1 in subjects with CF who have the *G551D-CFTR* mutation and mild lung disease

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Objectives: This study assessed the use of LCI as a more sensitive measure of improvement in lung function in subjects with FEV_1 in the normal range
Methods: This Phase 2, randomized, double-blind, placebo-controlled, multicenter, crossover study evaluated the effect of ivacaftor on LCI derived from multiple breath washout of SF6 using an open system Innocor device. Key inclusion were age ≥6 years, a *G551D-CFTR* mutation on at least one allele, FEV_1 >90% predicted, and LCI >7.4 (upper limit of normal). Ivacaftor 150 mg or placebo was administered q12h for two 4-week periods with a 4-week washout in between.
Results: Mean (SD) baseline parameters for the 20 randomised patients were 16.6 (10.9) years for age, 9.0 (1.5) for LCI and 97.2 (10.6) percent predicted for FEV_1. The treatment effect of ivacaftor for adjusted mean change from baseline in LCI at Day 29 was -2.07 (P=0.0004) whereas the mean change from baseline in FEV_1 was 7.0% (P=0.0117). Treatment difference for the mean change from baseline in sweat chloride was -45.8 mmol/L ($P<0.0001$). In the ivacaftor period, adverse events were reported in 13 subjects and serious adverse events in 2 subjects; the correspondent changes in the placebo period, were AEs in 15 and SAEs in 1 subject.
Conclusions: In subjects with CF who have mild lung disease, ivacaftor treatment improved ventilation inhomogeneity as measured by LCI and respiratory function as measured by percent predicted FEV_1. Adverse events were consistent with previous ivacaftor studies and mostly related to manifestations of CF.
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Long-term safety and efficacy of ivacaftor in subjects with CF who have the *G551D-CFTR* mutation

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Objectives: Ivacaftor was evaluated in 2 48-week Phase 3 studies. This 96-week open-label extension (PERSIST) evaluated the safety and efficacy of long-term ivacaftor in subjects who completed the prior trials (STRIVE and ENVISION).
Methods: 192 subjects who completed treatment in STRIVE or ENVISION enrolled in PERSIST. All subjects received ivacaftor 150 mg q12h in addition to prescribed therapies. Here we report the results of 96 weeks of treatment for subjects who were in STRIVE (n=144) and 72 weeks for those in ENVISION (n=48).
Results: For subjects who received ivacaftor in the placebo-controlled studies, the FEV_1 improvements were sustained in PERSIST. For STRIVE subjects, the mean (SD) absolute change from STRIVE baseline in % predicted FEV_1 was 9.4% (8.3%) on Day 1 of PERSIST (Week 48 in STRIVE), 10.3% (9.3%) at Week 72, and 9.5% (10.1%) at Week 96. For ENVISION subjects, the mean (SD) absolute change from ENVISION baseline was 10.2% (15.7%) on Day 1 of PERSIST, 9.1% (15.6%) at Week 60, and 10.1% (14.2%) at Week 72. For placebo subjects in STRIVE or ENVISION, the FEV_1 improvements in PERSIST were similar to those observed in ivacaftor subjects during the placebo-controlled studies. The mean (SD) absolute change from PERSIST baseline was 9.4% (8.5%) at Week 96 for STRIVE placebo subjects and 8.1% (12.5%) at Week 72 for ENVISION placebo subjects. The safety profile observed in PERSIST was generally consistent with the safety profile observed during ivacaftor treatment in STRIVE and ENVISION.
Conclusions: Ivacaftor-related improvements in lung function were sustained with additional ivacaftor treatment. No new clinically important safety concerns were identified.
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Inhaled glutathione tolerability and efficacy in patients with cystic fibrosis

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In CF patients, Glutathione (GSH), the first-line defence of lungs against oxidative stress, is severely reduced. A randomized, single blind controlled trial of inhaled GSH vs placebo (NCT01450267) is underway to evaluate the effect of GSH in a cohort of CF patients.
94 CF patients (48 F, median age 20.8 years) in regular follow up at the Regional Pediatric and Adult CF Center of Naples, were enrolled, 50 patients (23 F) were

randomly assigned to the GSH group and 44 (25 F) to the placebo group. The inclusion criteria were: CF diagnosis by sweat test and/or two CF causing mutations, age of patients >6yrs, FEV1% >40% of the predicted value, negative culture for Burkholderia Cepacia. Spirometry was performed before, 10 and 60 minutes after GSH inhalation test (10 mg/kg, maximum dosage 600mg/dose) in order to assess tolerability. Follow-up visits including spirometry took place one, three, six, nine months and after the end of treatments.
No patients showed a decrease in FEV1% >15% after GSH inhalation. In the subgroup of CF patients (n=27) with an obstructive ventilatory defect (FEV1/FVC<88%) six months therapy with GSH determined a statistically significant increase in FEV1% (58.3±13.2 vs 62.6±15.1 p =0.048) compared to the group (n=20) treated with placebo (59.3±14.9 vs 56.8±18.4).
Preliminary results suggest that inhaled GSH is well tolerated and determines an improvement in the respiratory function in CF patients.

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Assessment of lung function in pre-school children with cystic fibrosis by nitrogen washout

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Pulmonary function in young children can identify the early manifestations of diseases like cystic fibrosis (CF) and prompt to early intervention. We evaluated in pre-school age children the performance of ventilatory indices obtained from N2 washout (FRC, LCI, Scond, Sacin) as to their feasibility and ability to detect differences between disease and control groups. N2 washout was performed with a novel system that utilizes an ultrasonic flow sensor as well as O2 and CO2 sensors (Exhalyzer, EcoMedics AG). N2 washout was performed during tidal breathing and using 100% Oxygen. Three maneuvers free of artifact were obtained whenever possible and allowing for 2-times the washout time to lapse between maneuvers. This was followed by spirometry and aiming to obtain at least 3 valid flow volume loops. Study groups included children ages 3 to 6 year old with CF (n=20) and asthma (AS, n=15), as well as a group of healthy controls (HC, free from history of respiratory disease or cigarette smoke exposure). Children were studied at a period of freedom from any acute symptomatology. Research quality Nitrogen washout could be completed in 90% of CF, 75% of AS and 70% of HC. FRC was comparable between the groups (p=0.1). The LCI from the N2 washout was elevated in CF with a mean of 10.4±2.6, as well as Scond 0.05±0.03 and Sacin 0.5±0.5, which was statistically significant from the other 2 groups ($p<0.05$). We conclude that N2 washout can be completed without difficulty even in children that have little familiarity with pulmonary function testing. Indices obtained from the N2 washout can detect defects in ventilatory function in children with CF that distinguishes them from other children.

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Alternative multiple breath washout outcomes for clinical trials in cystic fibrosis

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The Lung Clearance Index (LCI) is a sensitive marker of early lung disease. and LCI, but not spirometry, was able to detect treatment effects of hypertonic saline in CF patients with mild disease (Amin et al; Thorax 2010). We used data from this interventional trial to investigate whether any other outcomes of the multiple breath washout could detect treatment effects similar to LCI. Using a cross-over design, patients were randomized to either hypertonic saline or isotonic saline in a randomized sequence, separated by a 4 week washout period. MBW was measured in triplicate by mass spectrometry (AMIS 2000; Innovision A/S, Odense, Denmark) using a gas mixture containing 4% SF_6, 4% He, 21% O_2 and balanced N_2. The current analysis includes 15 subjects for whom the following additional outcome measures could be assessed: normalized concentration of end tidal tracer gas (Cnet) at 6 turnovers (6T0), moment ratios (M1M0, M2M0) and LCI measured by helium. No significant treatment effects were observed for LCI measured with helium as a tracer gas. For SF_6, unlike the LCI, Cnet at 6TO was not able to detect a treatment effect of hypertonic saline. Moment ratios showed different results depending on the ratio chosen; M1M0 was significantly lower for hypertonic saline at 1/40th the starting SF_6 concentration, whereas both M1M0 and M2M0 demonstrated a significant treatment effect when 6TO was used as the washout end point. These findings suggest that moment ratios, which may be less sensitive to variations in respiratory rate and tidal volume, may provide a complementary outcome to the LCI in clinical trials.
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Evaluation of the peripheral airway microstructure in children with cystic fibrosis (CF) using ^{3}He magnetic resonance imaging

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Background: Pathology and lung function studies show that small airways are affected early in CF lung disease. Due to the inaccessibility of the distal air spaces little research has been performed in this area. The lung microstructure can be studied using the relatively new technique of hyperpolarised noble gas magnetic resonance (^{3}HeMR) scanning(1).
Study aims: To compare acinar airway size of children with CF with that of healthy controls.
Methods: In children with relatively mild CF lung disease ^{3}HeMR was undertaken during breath-hold following inhalation of a bolus of hyperpolarised ^{3}He gas mixture. A signal was obtained using the q-space technique(2). We applied Yablonskiy's acinar model(3) on the raw data to obtain the values for mean acinar duct diameter, R and mean alveolar sleeve depth, h. All children had spirometry and lung clearance index (LCI) measured.
Results: We studied 9 children (6-10y) with CF (FEV1: 97.6%predicted; SD ±14.3) and 18 age-matched controls. LCI was elevated in all CF patients (median 10.7; range 9.1-12.9). Acinar duct diameters (438.4μm; SD ±21.8) and alveolar sleeve depth (294.2μm; SD ±60.3) were both significantly ($p<0.05$) larger compared to controls (404.3μm; SD ±34.8 and 223.8μm; SD ±38.5 respectively).
Discussion: ^{3}HeMR is well tolerated in children from school age. We found that R and h, both surrogate values for acinar size, are larger in children with mild CF lung disease compared to healthy controls. ^{3}HeMR may constitute a sensitive technique for investigating CF lung disease.
References:
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