Background: Cystic fibrosis (CF) is the most common lethal autosomal recessive genetic disease in the Caucasian population. The CF gene, identified in 1989, encodes a cell membrane ion channel (CFTR), which, when absent or functioning poorly, leads to dehydrated periciliary fluid, thickened mucus, and chronic bacterial infection in the airways. Currently, treatment in CF is focused on mucus clearance, infection control, and nutritional support. Ivacaftor is in a new class of drugs designed to treat the underlying molecular defect in CF by increasing the function of the defective CFTR protein and restoring ability to transport ions across the cell membrane. The action of ivacaftor is specific to a limited number of “gating” mutations, most notably the G551D mutation, which represents approximately 4% of CF alleles.

Purpose: To determine whether hyperpolarized helium-3 (HHe) MR ventilation imaging can detect the effect of treatment with ivacaftor in subjects with CF and the G551D mutation.

Methods and Materials: We performed a single blind, placebo-controlled, Phase 2 investigational study of ivacaftor designed to evaluate HHe MR imaging as a clinical endpoint in CF trials. Subjects were 12 years or older with CF, and had a G551D mutation on at least one allele and an FEV1 of ≥40% predicted. A total of 8 subjects completed the trial. Subjects underwent spirometry and HHe MRI every 2 weeks for 8 weeks (days 0, 14, 28, 42, and 56). Drug dosing consisted of a placebo lead-in from days 0 to 14, treatment with ivacaftor (150 mg q12h) from day 14 to day 42 (28 days), followed by a placebo washout of 14 days from day 42 to day 56.

Helium-3 gas was polarized using a prototype commercial system (Magnetic Imaging Technologies Inc., Durham, NC), and polarizations between 20% and 40% were achieved. For each HHe MR acquisition, a 1 or 2 liter plastic bag (Jensen Inert Products, Coral Springs, FL) was filled with between 300 and 600 cc of HHe and enough nitrogen to total approximately 1/3 of the subjects FVC. The subject inhaled the HHe through a small plastic tube attached to the bag containing the gas, and three-dimensional (3D) helium-3 and proton image sets of the lung were acquired during a single breath hold using a 1.5T whole-body MRI system (Avanto, Siemens Healthcare, Malvern, PA) and a linearly-polarized transmit/receive RF coil tuned to the helium-3 frequency (Rapid Biomedical, Rimpar, Germany). The 3D steady-state free precession (TrueFISP) helium-3 and proton acquisitions had the following parameters: TR/TE 1.9/0.8 ms (helium-3) or 1.8/0.7 ms (proton), flip angle 9°, isotropic 3.9-mm spatial resolution. Elliptical k-space sampling and partial Fourier were used for both methods, resulting in a total breath-hold time of approximately 12 s. The MR images were analyzed using an automated method to quantify the ventilated lung volume on HHe MRI. The co-registered proton images were used to segment the lung boundaries, and following a bias correction, the lungs on the HHe images were divided into well and poorly ventilated regions.

Results: An interim analysis of the first 4 subjects* [mean age 20 years; mean FEV1 at screening 80% predicted, (range 62-100% predicted)] demonstrates that following 28 days of treatment with ivacaftor the total volume of poorly ventilated lung decreased in all four subjects, with the gas appearing to be more homogeneously distributed within the lungs (Figure 1). The majority of this effect occurred within 14 days of treatment (Figure 2). Following the 14 day washout period, the poorly ventilated volume returned to near baseline as had FEV1, indicating both a rapid onset of action of ivacaftor and a rapid return to pathology after cessation of therapy. Interestingly, Subject 3, who had the highest baseline FEV1 %pred, had a substantially greater improvement in poorly ventilated lung volume than improvement in FEV1, suggesting HHe MRI may be more sensitive to treatment effects than FEV1 in subjects with normal spirometry. Another interesting finding was that the location and size of ventilation defects is not random between consecutive imaging but defects occurred, disappeared and then reoccurred at fixed locations in individual subjects.

Discussion: To our knowledge this is the first study in human subjects to show that HHe MRI can demonstrate the efficacy of an investigational drug. These results suggest that HHe-MRI may be a sensitive measure of lung dysfunction and therapeutic response in CF, and possibly other pulmonary disorders. Larger, longer-term studies are underway to further define this potential in pediatric and adult subjects.

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*The complete analysis of all 8 subjects will be available soon.