

Single Dose Escalation Study to Evaluate Safety of Nasal Administration of CFTR001 Gene Transfer Vector to Subjects with Cystic Fibrosis

TECHNICAL ABSTRACT

Cystic Fibrosis (CF) is a serious, inherited disease that primarily results in lung disease. Lack of function of a protein called Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is responsible for the disease. This is a double blind, placebo-controlled, dose-escalation trial of compacted DNA administered to the nasal epithelium of patients with cystic fibrosis. The primary goal of the study is to investigate the safety and tolerability of administering these polylysine-DNA complexes stabilized with polyethylene glycol to the human nasal epithelium by superfusion. Particular attention will be paid to investigating inflammatory responses to the complexes, as well as broad-based evaluation of systemic toxicity. The secondary goal of the study is to determine the extent of gene transfer to the nasal epithelium. Measurement of CFTR gene transfer will be determined by several methods: 1) expression of plasmid CFTR DNA can be detected by measuring the nasal potential difference; 2) RT-PCR in nasal epithelial cells retrieved from the subject; and 3) increased expression of nitric oxide synthase-2, which is down regulated in cystic fibrosis nasal epithelium, will be measured by immunostaining. Adult patients with cystic fibrosis with FEV1 \geq 50% predicted will be evaluated prior to treatment with nasal potential difference measurements, history and physical examination, pulmonary function tests, hematologic evaluation, and serum chemistries. Those who qualify will be treated with a single dose of vector (2 ml) in one nostril and vehicle (2 ml) in the other, superfused by the investigator onto and below the inferior turbinate, under direct visualization. Neither the investigators nor the patients will know which nostril received which treatment. Subjects will be followed very closely after nasal instillation. These follow-up evaluations will include physical examinations, nasal potential difference measurements, nasal washings to evaluate inflammatory response, blood chemistries to evaluate activation of serum complement and the general state of health, hematologic evaluation, and pulmonary function tests. The initial dose will be 0.080 mg DNA. If no significant toxicity is observed, subsequent subjects may have the dosage amount increased according to the protocol. Doses will escalate by increments until the maximum dose of 8 mg is reached. The trial will be concluded when the highest dose planned has been administered, or when adverse events of grade 2 or higher have occurred in at least three subjects at a lower dose level (this dose then becomes the maximum tolerated dose).