

1.0 SCIENTIFIC ABSTRACT OF THE PROTOCOL

Cystic fibrosis (CF), the most common lethal genetic disease in North America, is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene product is required for regulation of epithelial chloride transport in multiple organs, including the airways. CF lung disease develops gradually over many years as abnormally viscous secretions that lead to airway obstruction, infection, inflammation, and fibrosis. It ultimately may lead to respiratory failure, which is the cause of death in greater than 90% of CF patients. It is thought that correction of the underlying CFTR gene defect may result in therapeutic effect on the progressive lung disease.

The vector (tgAAVCF) is derived from Adeno-Associated Virus (AAV), which is not known to cause human disease. This transducing vector can be generated at sufficiently high titers that it is practical as a delivery system and vector preparation can be purified to near homogeneity, removing contaminants and process materials.

Furthermore, AAV-CFTR vectors transduce and express recombinant CFTR in vivo after delivery to the airway surface of animals. Long-term vector expression, up to 6 months after a single-dose administration, has been observed in the New Zealand white rabbit and rhesus monkey models. Administration of higher doses of tgAAVCF by aerosol inhalation to rhesus macaques has demonstrated dose-dependent gene transfer and gene expression. Repeat dose administrations at these higher doses were well tolerated, and dose dependent gene transfer was observed. In some animals, serum neutralizing antibody titers to AAV2 increased and low titers of antibody and an elevation of lymphocytes were observed in bronchial wash fluid. There was no other clinical pathology or histologic findings related to the exposure of vector. Biodistribution of the vector to the gonads was not observed.

Over 60 cystic fibrosis patients, to date, have been administered single doses of tgAAVCF with no serious adverse events. Data from administration to the maxillary sinus, nose, lung lobe, and whole lung have shown a dose dependent, persistent gene transfer following single dose administration. A number of functional measurements, including sinus potential difference measurements and changes in

IL-8 levels are suggestive of biological activity although vector messenger RNA (mRNA) has not yet been detected in human clinical trials to date

This study is designed to test whether multiple dose aerosol administration of tgAAVCF is safe, well tolerated, and whether tgAAVCF has effects on lung function and inflammation. A major goal of this study is to explore possible clinical endpoints and determine their potential in measurement of efficacy for this product. The therapeutic goal, in the adult population will be to reverse halt or delay disease progression while a prophylactic approach will be used for children.

A total of 24 patients are planned to be enrolled: 18 patients will receive active drug and six patients will receive placebo. tgAAVCF, at a dose of 1×10^{13} DNase-resistant particles (DRP) will be directly administered (one dose every four weeks) to the whole lung by oral inhalation of aerosolized vector, using the Pari LC Plus™ nebulizer to male and female CF patients ($FEV_1 \geq 60\%$; clearly defined CF, and must be ≥ 15); planned to change to ≥ 12 when bronchoscopy period of trial completed. A safety review by the Therapeutics Development Network Drug Safety Medical Board (TDN-DSMB) is planned after the second dose has been administered to all patients in the first cohort. Following this review, enrollment and dosing of the remaining patients will be concurrent. After eight patients have received at least one dose of study agent, and if the DSMB has determined that there are no significant safety findings that would preclude enrollment of younger patients, then the minimum age will be reduced to 12 years of age.