Safety, immunogenicity and pharmacokinetics (PK) of a 120 mg/kg/week dose of alpha_1-proteinase inhibitor in alpha_1-antitrypsin deficiency

Dr. Michael Campos MCampos1@med.miami.edu MD 1, Friedrich Kueppers Friedrich.Kueppers@tuhs.temple.edu 2, James Stocks James.Stocks@uthct.edu 3, Charlie Strange strangec@musc.edu 4, Junliang Chen junliang.chen@grifols.com 5, Rhonda Griffin rhonda.griffin@grifols.com 5, Laurene Wang-Smith lws@indapharma.com 6, Maria Cruz Maria.Cruz@grifols.com 5, Pete Vandeberg pete.vandeberg@grifols.com 5 and Mark Brantly Brantly@medicine.ufl.edu 7.

1 Pulmonary Disease - Internal Medicine, University of Miami School of Medicine, Miami, United States; 2 Pulmonary Disease - Internal Medicine, Temple University Hospital, Philadelphia, United States; 3 Pulmonary Disease - Internal Medicine, University of Texas Health Science Center at Tyler, Tyler, United States; 4 Pulmonary Disease - Internal Medicine, Medical University of South Carolina, Charleston, United States; 5 Pulmonary Disease - Internal Medicine, Grifols Therapeutics Inc, NC, United States; 6 Pulmonary Disease - Internal Medicine, INDAPharma, LLC, NC, United States; and 7 Pulmonary Disease - Internal Medicine, University of Florida College of Medicine, Gainesville, United States.

Body: Background: The approved dose of alpha_1-proteinase inhibitor (alpha_1-PI) for treating alpha_1-antitrypsin deficiency (AATD) is 60 mg/kg/week intravenously (IV). Although this dose aims to increase serum alpha_1-PI levels above a proposed “protective” threshold (11mM), it is still below the normal range in healthy subjects. We report the safety, tolerability, and PK parameters of 120 mg/kg/week IV alpha_1-PI (Prolastin®-C). Methods: In this double-blind crossover study, 30 symptomatic AATD patients were randomly assigned to 60 or 120 mg/kg/week IV Prolastin®-C for 8 weeks, and then changed to the alternate dose after a 2-week washout period. Adverse events (AEs) were recorded, plasma was tested for anti-drug antibodies (ADA) and PK parameters of alpha_1-PI were measured. In addition, a neutralizing antibody ELISA was developed and validated for potential characterization of ADAs. Results: The higher dose was well tolerated by all subjects and the frequency of AEs did not appear to be dose-dependent. Exacerbation of COPD was the most frequent AE, consistent with the subjects’ diagnoses. Mean steady-state trough serum alpha_1-PI concentration after the 120 mg/kg weekly dose was higher than that after the 60 mg/kg dose (27.7µM and 17.3µM, respectively). Plasma samples tested negative for anti-Prolastin®-C antibodies with a screening/confirmatory ELISA assay. Conclusions: The 120 mg/kg/week dose of Prolastin®-C was well tolerated, did not result in an immunogenicity response and achieved favorable physiologic alpha_1-PI serum levels. Assessment of the clinical efficacy of this higher dose on the symptoms and progression of AATD is warranted.