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INHALED ALPHA$_1$-PROTEINASE INHIBITOR THERAPY IN PATIENTS WITH CYSTIC FIBROSIS

Amit Gaggar, MD, PhD[1], **Junliang Chen, PhD**[2], **James F Chmiel, MD**[3], **Henry L Dorkin, MD**[4], **Patrick A Flume, MD**[5], **Rhonda Griffin, RN**[2], **David Nichols, MD**[6], and **Scott H Donaldson, MD**[7]

[1]University of Alabama at Birmingham, Birmingham, AL, United States

[2]Clinical Development, Grifols, Bioscience Industrial Group, Research Triangle Park, NC, United States

[3]Division of Pediatric Pulmonology, Case Western Reserve University School of Medicine and Rainbow Babies and Children's Hospital, Cleveland, OH, United States

[4]Harvard Medical School, Boston, MA, United States

[5]Medical University of South Carolina, Charleston, SC, United States

[6]National Jewish Health, Denver, CO, United States

[7]University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, United States

Abstract

Background—Inhaled alpha$_1$-proteinase inhibitor (PI) is known to reduce neutrophil elastase burden in some patients with CF. This phase 2a study was designed to test inhaled Alpha-1 HC, a new aerosolized alpha$_1$-PI formulation, in CF patients.

Methods—We performed a randomized, double-blind, placebo-controlled study and evaluated the safety of 100 or 200 mg of inhaled Alpha-1 HC once daily for 3 weeks in subjects with CF. Thirty adult subjects were randomized in a 2:1 ratio to receive Alpha-1 HC or placebo.

Results—Drug delivery was confirmed by a dose-dependent increase in the sputum alpha$_1$-PI. Seven (20.0%) of the 35 adverse events in the 100-mg dose group, 3 (13.0%) of 23 in the 200-mg dose group, and 4 (14.3%) of 28 in the placebo group were drug-related in these subjects. One serious adverse event occurred in 1 subject within each group.

Conclusions—Alpha-1 HC inhalation was safe and well tolerated.

Introduction

Cystic fibrosis (CF) lung disease is characterized by viscous mucus, chronic respiratory infections, and a sustained exaggerated inflammatory response [1]. Airway recruitment of neutrophils causes airway tissue destruction and remodeling through excess release of

Corresponding author: Rhonda Griffin, RN, Associate Director, Clinical Development at Grifols, Bioscience Industrial Group, 79 TW Alexander Drive, Bldg 4201, Research Triangle Park, NC 27709, Phone: 919-316-6693, Rhonda.Griffin@grifols.com.

neutrophil elastase (NE) [2–4]. Endogenous alpha$_1$-proteinase inhibitor (alpha$_1$-PI), which inhibits NE activity, is overwhelmed by excess release of NE in patients with CF [2–5]. This protease/antiprotease imbalance results in a progressive decline in lung function, in part through airway remodeling [2, 3, 6]. There is no specific antiprotease treatment available for patients with CF [2, 7]. The potential protective function of alpha$_1$-PI provides a strong rationale to develop chronic antiprotease therapies to control airways inflammation and tissue damage.

Human plasma-derived alpha$_1$-PI has a well-established safety profile when administered intravenously in patients with alpha$_1$-antitrypsin deficiency, a condition characterized by increased serine protease activation leading to early-stage emphysema [8–11]. Aerosolized delivery of alpha$_1$-PI by inhalation permits delivery of drug to the site of active airway disease while limiting systemic exposure [12] and has been shown to reduce NE burden and inflammation in respiratory secretions of alpha$_1$-antitrypsin–deficient patients [13–15]. In previous studies, aerosolized alpha$_1$-PI has been found to be both safe and well tolerated in patients with CF [3, 6, 16–18]. However, an effective combination of delivery system and drug is required to efficiently deposit aerosolized alpha$_1$-PI in a sufficient dose at the site of CF lung disease. The AKITA$^{2®}$ APIXNEB™ (Vectura Group plc, Chippenham, United Kingdom) electronically regulated nebulizer system increases drug deposition compared with older nebulizer systems and allows for accurate dosing that is independent of lung function impairment. This is achieved by customizing and controlling the patient's breathing pattern [16]. Therefore, it is hypothesized that the combination of a well-tolerated alpha$_1$-PI preparation and an electronically regulated nebulizer system may provide improved deposition of a biologically relevant antiprotease. Here, we report results of a 3-week phase 2a study conducted to evaluate the safety and tolerability of inhaled Alpha-1 Hydrophobic Chromatography Process (HC) in patients with CF.

Subjects and Methods

Subjects

This study enrolled men and women aged ≥18 years with CF, as evidenced by 1 or more clinical features consistent with the CF phenotype and 1 or both of the following: (1) sweat chloride level ≥60 mEq/L by quantitative pilocarpine iontophoresis test; (2) 2 well-characterized mutations in the CF transmembrane conductance regulator (CFTR) gene. Subjects were required to have a prebronchodilator forced expiratory volume in 1 second (FEV_1) ≥40% of predicted at screening and have a FEV_1 that was ≥40% of predicted and within ±15% of the screening FEV_1 value prior to study drug administration on day 1 of the study.

Key exclusion criteria included an investigator-defined pulmonary exacerbation either 4 weeks before screening or between screening and randomization that required antibiotic treatment; respiratory insufficiency; significantly elevated liver enzymes; history of smoking; any lung surgery; positive culture for *Burkholderia cepacia* or *mycobacterium*; or active allergic bronchopulmonary aspergillosis. Other major exclusions used in this study are provided in the supplementary material.

Study design and procedure

This was a multicenter, sequential dose escalation, randomized, double-blind, placebo-controlled phase 2a study (ClinicalTrials.gov: NCT01684410). Alpha-1 HC (100 mg and 200 mg) was administered once daily and compared with placebo over a 21-day treatment period. All subjects provided written informed consent. The study was approved by the institutional review board and conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki [19, 20].

Two sequential dosing cohorts (100 mg and 200 mg) were enrolled (Figure S1). In each cohort, subjects were randomized in a 2:1 ratio utilizing a block size of 3 to receive Alpha-1 HC (50 mg/ml) or a volume-matched placebo delivered once daily via the AKITA^2 nebulizer system. Inhalation data (eg, start of inhalation, duration of treatment, daily dose compliance) was recorded by the AKITA^2 device. Subjects were considered adherent to study medication if they had taken at least 80% of the prescribed dose over the total duration of study drug dosing. A review of unblinded safety results from the Alpha-1 HC 100 mg treatment cohort was conducted by the Cystic Fibrosis Foundation Therapeutics Data Monitoring Committee prior to proceeding to the next cohort. Screening occurred 14 ± 7 days prior to study treatment initiation. A follow-up visit occurred approximately 28 days following the treatment period in each cohort.

Safety assessments

Data were collected for evaluation of safety from the time of consent until the final study visit. A detailed description of treatment-emergent adverse event (TEAE) and serious adverse event (SAE) data collection are provided in the supplementary material.

Subjects were monitored via weekly telephone calls. Pulmonary exacerbations were graded as mild (increase in 1 or more symptoms [dyspnea, cough, and/or sputum] that was controlled by increasing usual medication), moderate (required outpatient antibiotic treatment) and severe (resulted in hospitalization). Subjects treated with Alpha-1 HC were tested for immunogenicity with an antibody screening enzyme-linked immunosorbent assay to alpha$_1$-PI at screening, study day 22, and at follow-up. Abnormal test values that were judged relevant by the investigator were considered adverse events (AEs). Adverse events, which were related to the AKITA^2 nebulizer system, were reported based on the investigator's judgment (see supplementary material).

Exploratory efficacy variables

The exploratory objectives included possible signals of treatment efficacy, subject satisfaction with aerosol treatment, and health-related quality of life (HRQOL). The exploratory variables included assessment of changes from baseline following treatment for pulmonary function tests (PFTs; FEV_1, FEV_1% predicted, and forced vital capacity [FVC]), and sputum analyses of alpha$_1$-PI levels, NE activity, bacterial culture, leukotriene B4 (LTB4) concentration, inflammatory cell counts (absolute and differential counts), pro-inflammatory cytokines (interleukin [IL]-6, -8, and -17; IL-1 beta, and tumor necrosis factor-alpha [TNF-α]), and urine markers of lung injury (desmosine and isodesmosine).

Sputum for alpha$_1$-PI level, sputum biomarkers of inflammation and blood biomarkers of inflammation were collected at screening, randomization (day 1), day 10, at the end of treatment (day 22), and at the end of the 4-week follow-up phase. Urine samples were collected at screening, day 10, at the end of treatment, and at follow-up. Forced expiratory volume in 1 second and FVC were assessed at screening; before and after daily treatment on days 1, 2, and 10 during the 3-week treatment period; at the end of treatment (day 22); and after a 4-week follow-up period. The Subject Satisfaction Survey regarding the aerosol treatment and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) [21] were assessed by a written questionnaire. The Subject Satisfaction Survey was completed at the end of treatment visit and a by-subject list of responses to each question was analyzed by treatment group and overall. The CFQ-R was completed at randomization and the end of treatment visit (day 22). CFQ-R scores and the change from baseline in scores were analyzed by treatment group for each domain.

Statistical analyses

Thirty subjects were analyzed via 3 defined populations: safety population (subjects that received any dose of study drug), intent-to-treat population (all randomized subjects), and per-protocol population (subjects who were randomized, completed investigational product treatment, had no major protocol deviations affecting sputum analysis, and had both baseline and end-of-study sputum results). For the purpose of analysis, placebo subjects from both cohorts were pooled and all analyses were summarized by 3 treatment groups (Alpha-1 HC 100 mg, Alpha-1 HC 200 mg, and placebo).

Descriptive statistics including the number of subjects, mean, median, standard deviation (SD), and minimum/maximum values were analyzed for quantitative variables. The number and percentage of subjects in each category were analyzed for categorical/ordinal variables.

Results

Disposition, demographics, and other baseline characteristics of subjects

The disposition of subjects is presented in Figure 1. All subjects were ≥80% adherent with study treatment as recorded by AKITA^2 device. Demographic and baseline characteristics were similar across the 3 treatment groups (Table 1).

Safety

Assessments of adverse events—Treatment-emergent AEs were generally similar across all treatment groups (Table 2). Treatment emergent AEs judged by the investigator as related to Alpha-1 HC were experienced by 5 subjects (50%) in the Alpha-1 HC 100 mg treatment group, 1 subject (10%) in the Alpha-1 HC 200 mg treatment group, and 2 subjects (20%) in the placebo treatment group. AKITA^2-related TEAEs were observed in 2 (20%) subjects (4 TEAEs) in the 100 mg Alpha-1 HC group, 1 (10%) subject (2 TEAEs) in the placebo group, and no subjects in the 200 mg Alpha-1 HC group. Serious AEs were reported by 1 subject in each treatment group: a pulmonary exacerbation was experienced by a subject in each of the Alpha-1 HC 100 mg and placebo treatment groups, both during the off-treatment follow-up phase and treated with inpatient antibiotic therapy. Abdominal pain

was reported as a TEAE in a subject 8 days after receiving Alpha-1 HC 200 mg. All 3 SAEs were moderate in intensity with abdominal pain (Alpha-1 HC 200 mg) and 1 pulmonary exacerbation (Alpha-1 HC 100 mg) described by the investigator as “not related” to the study drug and the other pulmonary exacerbation (placebo) considered “unlikely” due to the study drug. All 3 SAEs were considered not related to the AKITA^2 device by the investigator and were resolved following hospitalization. No subject discontinued from the study due to a TEAE and no deaths occurred.

Most frequent adverse events—The majority of TEAEs occurred only once within a treatment group with the most frequent TEAEs experienced in the respiratory, thoracic, and mediastinal disorders system organ class (Table 2). The most frequent TEAEs were hemoptysis, cough, wheezing, and pulmonary exacerbation (Table 2). A single pulmonary exacerbation was reported by 1 subject each (1/10, 10%) in the Alpha-1 HC 100 mg and placebo treatment groups and 3 subjects (3/10, 30%) in the Alpha-1 HC 200 mg treatment group.

Pulmonary exacerbations and clinical findings—The number of subjects with TEAEs—including pulmonary exacerbations, which were mild or moderate in intensity—was similar across treatment groups with at least 1 mild TEAE experienced by 7 subjects (7/10, 70%) in the Alpha-1 HC 100 mg treatment group, 5 subjects (5/10, 50%) in the Alpha-1 HC 200 mg treatment group, and 4 subjects (4/10, 40%) in the placebo treatment group. Three subjects each in the Alpha-1 HC 100 mg (3/10, 30%) and 200 mg (3/10, 30%) treatment groups and 2 subjects (2/10, 20%) in the placebo treatment group experienced moderate TEAEs.

There were a total of 5 pulmonary exacerbations: 1 subject each (1/10, 10%) in the placebo and Alpha-1 HC 100 mg treatment groups and 3 subjects (3/10, 30%) in the Alpha-1 HC 200 mg treatment group. Two subjects, both in the Alpha-1 HC 200 mg treatment group, experienced pulmonary exacerbations as defined by the investigator’s judgment; all remaining pulmonary exacerbations were defined by the Fuchs criteria [22]. As previously noted, 2 pulmonary exacerbations were reported as SAEs. No pulmonary exacerbations were graded severe by investigators and none resulted in early discontinuation. All pulmonary exacerbations were reported during the off-treatment follow-up period.

There were no clinically meaningful mean changes from baseline at any time point for clinical laboratory values, vital sign measurements, and physical exam findings (see supplementary materials).

Pulmonary function tests—Overall, no clinically meaningful mean changes from baseline in PFT values were identified (Table 3). Two subjects, both in the Alpha-1 HC 200 mg treatment group, exhibited a ≥20% decline in FEV_1 from baseline. One subject had a ≥20% decline in FEV_1 from baseline on study day 1 at 15 minutes and 1.5 hours postdose that resolved within 4 hours of receiving study drug. The second subject exhibited a ≥20% decrease in FEV_1 at the end-of-treatment visit (study day 22) but did not have any other postbaseline FEV_1 that was ≥20% lower than the baseline FEV_1. A single subject in the placebo treatment group had a TEAE of PFT decrease on follow-up that was reported as

mild in intensity and not related to the study drug or AKITA^2 device. No clinically relevant changes from baseline in peak flow measurement were recorded and none of the subjects recorded a postbaseline peak flow that was ≤30% of the baseline value.

Viral safety and immunogenicity—During the study, no subject tested positive for hepatitis A, B, or C; human immunodeficiency virus; or parvovirus B19 infection; and there were no reports of subjects exhibiting clinical signs and/or symptoms of viral infection. One subject administered Alpha-1 HC was positive for nonneutralizing anti-Alpha-1 HC antibodies, and this immunogenic response was determined to be transient in follow-up testing and did not lead to the development of any symptoms.

Exploratory variables—Pulmonary function tests provided both safety and exploratory efficacy endpoints in this study. No clinically meaningful changes were observed in these subjects (Table 3). Sputum analysis showed a notable increase in the alpha$_1$-PI level following study drug administration at randomization and study day 10 in the Alpha-1 HC treatment groups but not in the placebo treatment group. A larger increase in the mean sputum alpha$_1$-PI level was observed in the higher-dose (200 mg) treatment group (Table S1, Figure 2), suggesting a trend across doses. There were no notable differences between treatment groups or consistent trends over time in any treatment group for any other sputum parameters (NE activity, LTB4, IL-6, -8, and -17; IL-1 beta, and TNF-α) (Table S2) and inflammatory cell counts. Similarly, serum alpha$_1$-PI, blood inflammatory biomarkers (TNF-α, IL-6, IL-8, and IL-10) and urine desmosine and isodesmosine showed no noteworthy changes over time.

By a written questionnaire, most subjects (21/30) rated their effort to inhale from the AKITA^2 inhalation system as “normal” (11/30), “fairly easy” (6/30), or “very easy” (4/30). Most subjects (83.3%, 25/30) rated the airflow administered by the AKITA^2 device as “appropriate” and a majority of subjects (90%, 27/30) felt that the time to administer treatment with the AKITA^2 was “just right” and “somewhat quick.” However, a small percentage of subjects (10%, 3/30) felt that the time to administer treatment with the AKITA^2 device was “too long.” The actual recorded inhalation times for the 100 mg and 200 mg doses were 9.6 minutes and 15.1 minutes, respectively. The HRQOL assessed by CFQ-R completed by subjects at randomization and end-of-treatment visit showed no apparent quality-of-life differences, trends, or mean changes of note in total score or domain scores between treatment groups and within any treatment group.

Discussion

The results from the study provide important data supporting the safety of Alpha-1 HC administered for 21 days in subjects with CF. Although AEs were observed in the Alpha-1 HC and placebo treatment groups, none were dependent on the dose or showed consistent treatment dependency. Furthermore, TEAEs were mild or moderate in severity with no study discontinuations due to TEAEs. Of the 3 SAEs reported, only 1 (abdominal pain) started during the treatment phase with the actual hospitalization occurring 16 days after completion of the study treatment. The most frequent TEAEs were similar in the Alpha-1 HC and the placebo treatment groups, which suggests that Alpha-1 HC at either dose was safe and well

tolerated during the duration of the study by the subjects with CF. Other safety parameters reported as TEAEs—including physical examination findings, PFT measurements, laboratory tests, and vital signs—were not clinically meaningful for any treatment group and were not considered to be related to study drug.

Importantly, the delivery of inhaled Alpha-1 HC was reflected by increased $alpha_1$ antitrypsin levels in the sputum of patients, with a trend toward higher levels at the higher dose. These results strongly suggest the stability of the compound postnebulization and demonstrate that an electronically regulated nebulizer system such as the AKITA^2 device can effectively deliver Alpha-1 HC by aerosol in CF subjects, consistent with similar prior studies [4, 12]. The AKITA^2 inhalation system was well accepted by the subjects as indicated by survey results.

Aerosolized $alpha_{-1}$-PI has been shown to increase $alpha_1$-PI levels and decrease NE levels in subjects with CF [4, 6]. Although Alpha-1 HC did not reduce NE activity in the current study; unlike previous studies, this trial was not adequately powered to identify a decrease in NE activity [4], nor did it measure NE levels in the epithelial lining fluid, which is a more direct measure of active neutrophil elastase [6]. The inability to detect changes in blood and sputum inflammatory biomarkers as well as the breakdown products of NE in the urine (desmosine and isodesmosine) may be due to the short study duration as well as the small amount of Alpha-1 HC reaching the systemic circulation.

The current study was not powered to assess changes in FEV_1 or sputum $alpha_1$ antitrypsin (A1AT) concentrations; however, subsequent phase 2 and phase 3 studies could be sufficiently powered to analyze these parameters. Other opportunities for further phase 2 and phase 3 studies include a longer duration safety evaluation period, inclusion of patients with more severe respiratory insufficiency, and the delivery of Alpha-1 HC via alternative delivery devices.

In conclusion, daily Alpha-1 HC (100 mg or 200 mg) delivered for 3 weeks was safe, well tolerated, well accepted, and effective in raising the $alpha_1$-PI levels in the sputum of subjects with CF. These promising results suggest that Alpha-1 HC is effectively and safely delivered in patients with CF. However, future studies are needed to determine efficacy and potential use of Alpha-1 HC for chronic therapy in CF lung disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

This study was funded by Grifols Therapeutics Inc. J.F. Chmiel, P.A. Flume, D. Nichols, and S.H. Donaldson received grants from Grifols Therapeutics Inc. J.F. Chmiel was a member of the advisory board for Boehrigner Ingleheim, Genentech, and Gilead; member of the clinical research committee and a moderator of a symposium for the Cystic Fibrosis Foundation; member of the Pediatric Pulmonology sub-board for the American Board of Pediatrics; member of the executive committee for the American College of Chest Physicians; and consultant for KaloBios Pharmaceuticals and Celtaxsys. Junliang Chen and Rhonda Griffin are employees of Grifols, Bioscience Industrial Group.

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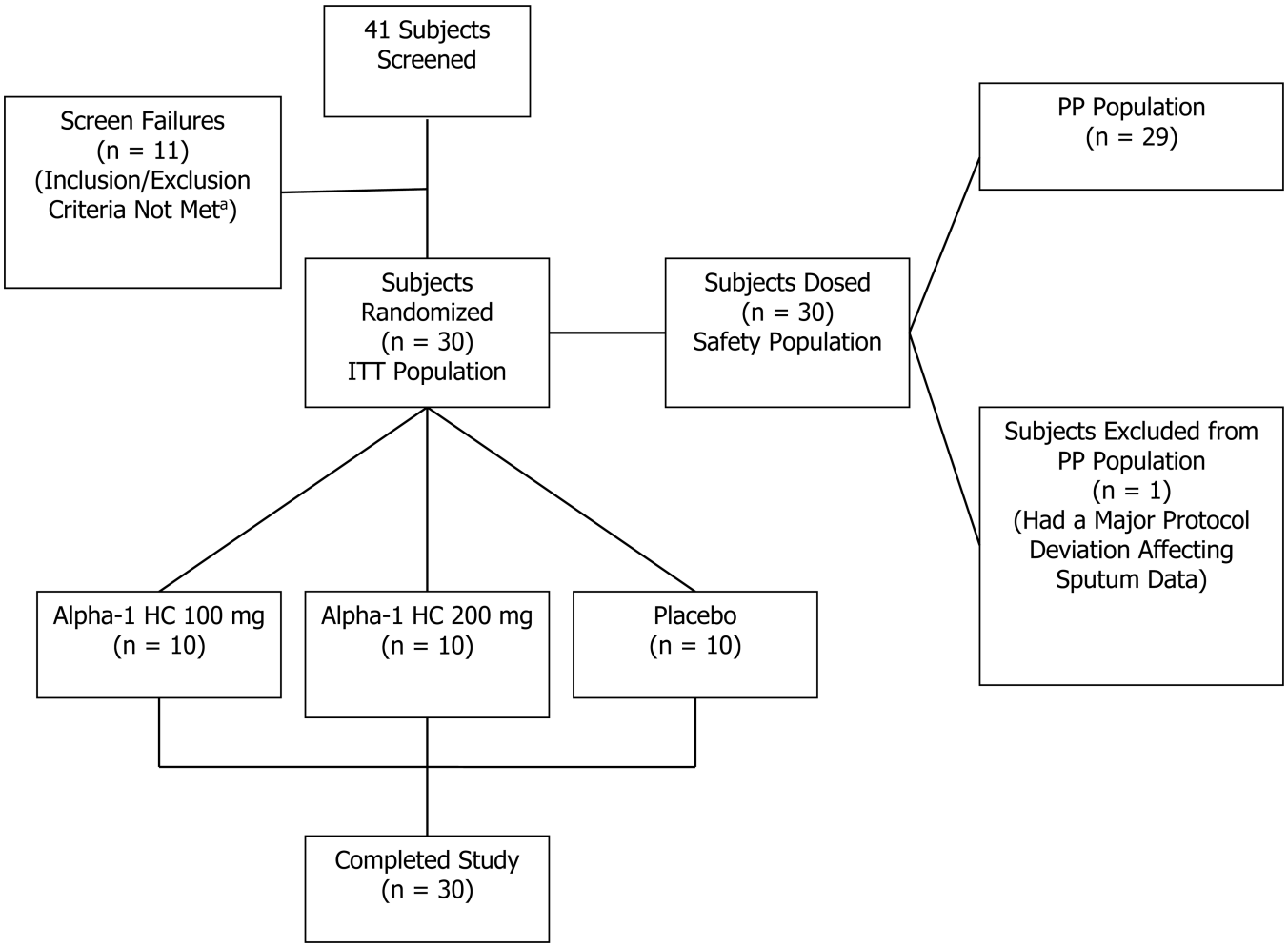

Figure 1.

Subject Disposition.

[a]Due to pulmonary function tests, pulmonary exacerbations, and problems with pretreatment sputum collection as defined in the inclusion/exclusion criteria.

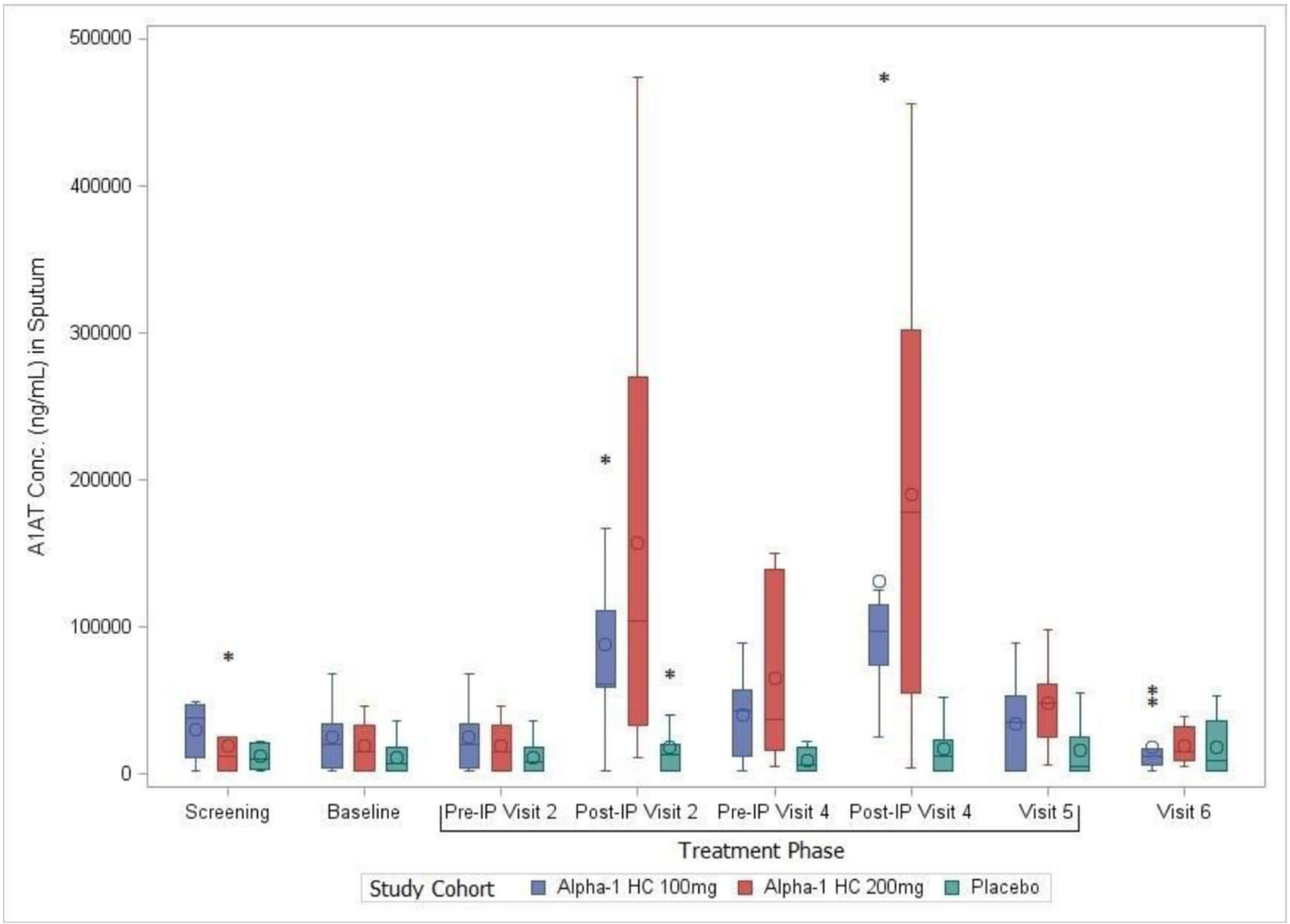

Figure 2.

Increase in the Alpha$_1$-PI Level in Sputum of Subjects Treated with Alpha-1 HC.

A1AT, alpha$_1$ antitrypsin.

O, mean; —, median within bars; *, outlier; boxes represent the range of 25%–75%.

Table 1

Subject Demographic and Baseline Characteristics.

Characteristic	Alpha-1 HC 100 mg (n = 10)	Alpha-1 HC 200 mg (n = 10)	Placebo (n = 10)
Sex, n (%)			
Female	8 (80)	6 (60)	6 (60)
Age, y			
Mean (SD)	28.2 (10.6)	28.1 (11.4)	29.3 (10.0)
Race, n (%)			
White	10 (100)	9 (90)	10 (100)
Multiracial	0	1 (10)	0
BMI (kg/m^2)			
Mean (SD)	23.7 (5.5)	22.3 (2.2)	22.3 (4.1)
Patient with known genetic mutation, n (%)			
Yes	9 (90)	10 (100)	10 (100)
No	1 (10)	0	0
Ever had a pulmonary exacerbation that required IV antibiotics, n (%)			
Yes	10 (100)	10 (100)	8 (80)
No	0	0	2 (20)
Positive respiratory culture within last 12 months, n (%)	10 (100)	10 (100)	10 (100)
FEV_1% predicted			
Mean (SD)	68.2 (21.51)	69.5 (24.94)	71.1 (21.71)

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

Table 2

Summary of subjects with AEs, most frequent AEs (≥3 subjects) and drug-related AEs.

	Alpha-1 HC 100 mg (n = 10)	Alpha-1 HC 200 mg (n = 10)	Placebo (n = 10)
Subjects with at least 1 TEAE	10 (100)	8 (80)	6 (60)
Subjects with drug-related TEAEs	5 (50)	1 (10)	2 (20)
Subjects with AKITA[2]-related TEAEs	2 (20)	0	1 (10)
Subjects with SAEs	1 (10)	1 (10)	1 (10)
Subjects with TEAE leading to discontinuation	0	0	0
Most frequent TEAEs occurring in ≥3 subjects within 1 treatment group			
Hemoptysis	4 (40)	1 (10)	1 (10)
Cough	3 (30)	1 (10)	1 (10)
Wheezing	3 (30)	1 (10)	0
Pulmonary exacerbation	1 (10)	3 (30)	1 (10)
Drug-related TEAEs			
Total number of drug-related TEAEs	7	3	4
Subjects with ≥1 drug-related TEAEs	5 (50)	1 (10)	2 (20)
Bronchospasm	0	0	1 (10)
Cough	0	0	1 (10)
Dry throat	1 (10)	0	0
Dyspnea	1 (10)	0	0
Hemoptysis	1 (10)	0	0
Oropharyngeal pain	0	0	1 (10)
Pulmonary exacerbation	0	1 (10)	0
Respiratory tract irritation	1 (10)	0	0
Sputum increased	1 (10)	0	1 (10)
Wheezing	1 (10)	0	0
Otitis externa	0	1 (10)	0
Otitis media	0	1 (10)	0
Decreased appetite	1 (10)	0	0

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Data presented as n (%).

Adverse events were linked to system organ class and preferred term by the Medical Dictionary for Regulatory Activities, Version 15.0. Subjects who had more than 1 event within a body system or assigned to the same preferred term were counted once.

Table 3

Pulmonary Function Tests.

	Alpha-1 HC 100 mg (n = 10)		Alpha-1 HC 200 mg (n = 10)		Placebo (n = 10)	
	Day 10 (4 h post-treatment)	**Day 22**	**Day 10 (4 h post-treatment)**	**Day 22**	**Day 10 (4 h post-treatment)**	**Day 22**
FEV_1 (L)						
Absolute change in mean from baseline (SD)	−0.025 (0.23)	0.008 (0.14)	−0.064 (0.32)	−0.086 (0.29)	−0.047 (0.18)	0.016 (0.18)
% Change in mean from baseline (SD)	1.2 (7.46)	1.5 (5.20)	0.6 (13.44)	−2.1 (12.28)	−1.5 (7.62)	0.5 (5.91)
FEV_1% predicted						
Absolute change in mean from baseline (SD)	−0.1 (5.84)	1.0 (3.83)	−1.9 (8.86)	−2.8 (8.27)	−1.2 (4.44)	0.3 (4.47)
FVC (L)						
Absolute change in mean from baseline (SD)	0.049 (0.16)	0.025 (0.13)	−0.013 (0.25)	−0.083 (0.42)	−0.011 (0.20)	−0.041 (0.15)
% Change in mean from baseline (SD)	2.0 (5.75)	1.2 (5.23)	0.1 (6.87)	−2.3 (11.57)	0.1 (5.14)	−0.9 (3.73)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

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