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SPARTA clinical trial design: Exploring the efficacy and safety of two dose regimens of alpha$_1$-proteinase inhibitor augmentation therapy in alpha$_1$-antitrypsin deficiency

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SPARTA;
CT densitometry

Summary
Background: Alpha$_1$-antitrypsin deficiency (AATD) is an underdiagnosed genetic disorder that results in early-onset emphysema due to low serum levels of alpha$_1$-proteinase inhibitor (alpha$_1$-PI), leading to increased activity of tissue-damaging neutrophil elastase. Clinical outcomes of AATD may be improved by administering alpha$_1$-PI augmentation therapy. Here, we describe the design of the ongoing **S**tudy of **P**rol**A**stin-c **R**andomized **T**herapy with **A**lpha-1 augmentation (SPARTA), a phase 3 trial designed to evaluate progression of lung tissue loss in patients with severe AATD receiving human alpha$_1$-PI (Prolastin®-C) versus placebo, using whole-lung computed tomography (CT) densitometry.
Study design: SPARTA is a randomized, placebo-controlled trial assessing the efficacy and safety of two separate doses of Prolastin-C (60 and 120 mg/kg) administered weekly over 3 years in patients aged 18–70 years with a diagnosis of AATD and clinical evidence of pulmonary emphysema. The primary measure of efficacy (change from baseline whole-lung 15th percentile lung density [PD15]) will be determined by CT lung densitometry measured at total lung capacity. Secondary efficacy variables will be the evaluation of severe chronic obstructive pulmonary disease exacerbations, as defined by American Thoracic Society/European Respiratory Society criteria, and PD15 of the basal lung region using CT densitometry. Adverse events will be collected and documented.

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Conclusions: The SPARTA trial is designed to evaluate the long-term (3-year) efficacy of 2 separate doses of Prolastin-C for the treatment of emphysema in patients with AATD.

Protocol number: GTi1201.

Clinical trials identifier: NCT01983241.

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Introduction

Alpha$_1$-antitrypsin (AAT) deficiency (AATD) is a genetic disease that results in emphysema and may occur in up to 3% of all patients with chronic obstructive pulmonary disease (COPD) [1—3]. This condition results from mutations in the *SERPINA1* gene encoding the serine protease inhibitor alpha$_1$-proteinase inhibitor (alpha$_1$-PI), with *PiS* and *PiZ* being the most commonly deficient alleles. Alpha$_1$-PI inhibits the human neutrophil elastase, which, in large quantities, can cause destruction of alveolar walls in the lung [4,5]. AATD disrupts the protease-antiprotease balance, leading to an excess activity of elastase and, consequently, tissue destruction. Inheritance of both *PiZ* alleles reduces alpha$_1$-PI serum levels to below the threshold level (11 μM) required for adequate neutrophil elastase inhibition [6,7], resulting in an increased risk for early onset of emphysema, particularly in patients who smoke. The mean age of diagnosis of AATD is 45.5 years, with 30.8% of patients being diagnosed over age 50 [3].

General principles to treat subjects with severe AAT deficiency with emphysema include: 1) avoidance of respiratory irritant substances, especially tobacco smoke; 2) supportive therapy, including medication (antibiotics, bronchodilators, and corticosteroids), cardiovascular conditioning and oxygen therapy, if clinically indicated; 3) surgery, including lung transplants and lung volume reduction surgery; and 4) treatment modalities targeting the molecular basis of AAT deficiency, including inhibition of polymerization of PiZZ or replacement of defective or absent genes, although the major focus of treatment for patients with emphysema due to severe AAT deficiency has been on correcting the deficiency by means of augmentation therapy [2,8,9,10]. Augmentation therapy with exogenous alpha$_1$-PI provides the opportunity for targeted AATD therapy [11,12]. Crystal and colleagues first tested the feasibility and safety of alpha$_1$-PI replacement therapy, suggesting that the most direct approach to therapy for AATD would be to replenish the missing protease inhibitor and thus re-establish the anti-neutrophil elastase protection for the lower respiratory tract [11]. Intravenous (IV) administration of Prolastin® (plasma-derived alpha$_1$-PI [human]) has been shown to increase serum levels of alpha$_1$-PI, and on the basis of this biochemical efficacy, Prolastin was the first alpha$_1$-PI approved for the treatment of patients with AATD [10]. Following its approval, other alpha$_1$-PI preparations were approved on the basis of bioequivalence to Prolastin, but controlled trials to demonstrate clinical efficacy were not conducted for any alpha$_1$-PI augmentation therapy [13,14].

Since the development of Prolastin, manufacturing processes have been modified to incorporate additional purification and pathogen-reduction steps to formulate Prolastin-C (alpha$_1$-proteinase inhibitor [human]), which has equivalent pharmacokinetics (PK) and a similar safety profile to Prolastin [15,16]. Currently, Prolastin-C is approved in the US, Canada, Colombia, and Argentina for 60 mg/kg weekly IV administration in patients with AATD and clinically evident emphysema [2].

Findings from various studies have provided results supporting the use of augmentation therapy in patients with AATD; however, there is a lack of scientific consensus regarding the clinical benefits of alpha$_1$-PI administration. Multiple retrospective and prospective studies have demonstrated that alpha$_1$-PI reduces lung function decline as measured by forced expiratory volume in 1 s (FEV_1), especially in patients with moderate lung dysfunction [17—19]. However, conflicting results from studies that have failed to demonstrate preservation of lung function with alpha$_1$-PI augmentation therapy [8,19] suggest the need for new studies and measures that can be used to accurately evaluate COPD progression. The use of computed tomography (CT) scans to evaluate the progression of emphysematous lung tissue has been evaluated in several studies (Table 1). An observational non-randomized study from the National Heart, Lung, and Blood Institute (NHLBI) Alpha1-Antitrypsin Deficiency Registry (ClinicalTrials.gov Identifier: NCT00005292) of 1129 subjects revealed a reduced risk of mortality in patients with AATD receiving augmentation therapy compared with those receiving no therapy [17,20,21]. Lung density measurements by CT scan have been shown to be a sensitive measure for assessing emphysema progression and as an outcome measure of emphysema-modifying therapy in patients with AATD [22,23]. The use of radiologic assessments as the primary efficacy endpoint is attractive in an orphan disease such as AATD where large numbers of patients would be required to demonstrate differences in more variable endpoints such as FEV_1 and pulmonary exacerbations. In November 2007, a draft guidance was published by the US Food and Drug Administration supporting the use of sensitive radiologic assessments as primary efficacy endpoints in COPD trials [24]. However, randomized, controlled clinical trials demonstrating the validity of CT endpoints in demonstrating the efficacy of alpha$_1$-PI products have not yet been done.

The **S**tudy of **Prol**A**s**tin-c **R**andomized **T**herapy with **A**lpha-1 augmentation (SPARTA) trial has been designed to fulfill the request by health authorities for conclusive data demonstrating the clinical efficacy of alpha$_1$-PI augmentation therapy for AATD-induced emphysema. To date, no dose-ranging studies have been conducted with any alpha$_1$-

Table 1 Characteristics of clinical trials to evaluate treatment with alpha$_1$-PI formulations in patients with AATD.

	Seersholm et al. [19]	NHLBI AATD Registry Study Group [17]	Wencker et al. [18]	Dirksen et al. [25]	Wencker et al. [26]	EXACTLE [23]	ChAMP [15]	SPARK [27]	SPARTA	RAPID [28]
Year Study design	1997 Prospective, multicenter, controlled, nonrandomized	1998 Prospective, multicenter, nonrandomized,	1998 Prospective, long-term, multicenter, nonrandomized	1999 Prospective, randomized, parallel, double-blind, placebo-controlled trial at 2 centers	2001 Multicenter, retrospective cohort	2009 Prospective, randomized, double-blind, placebo-controlled, parallel group	2010 Prospective, multicenter, randomized, double-blind, crossover	2013 Prospective, multicenter, randomized, double-blind, crossover	2013 Prospective, randomized, double-blind, placebo-controlled, parallel group	2014 Prospective, randomized, double-blind, placebo-controlled, parallel group
Number of patients	295	927	287	56	96	77	24	30	339	180
Experimental drug dosage and regimen	Prolastin 60 mg/kg weekly	Alpha-1 protease inhibitor formulation 60 mg/kg weekly	Prolastin 60 mg/kg weekly	Alpha-1 protease inhibitor formulation 250 mg/kg at 4-wk intervals	Prolastin 60 mg/kg weekly	Prolastin-C 60 mg/kg weekly	Prolastin-C 60 mg/kg weekly	Prolastin-C 120 mg/kg weekly	Prolastin-C 120 mg/kg weekly	Zemaira 60 mg/kg weekly
Comparator	No augmentation therapy	No augmentation therapy	N/A	Albumin (625 mg/kg) at 4-wk intervals	N/A	Placebo	Prolastin 60 mg/kg weekly	Prolastin-C 60 mg/kg weekly	Prolastin-C 60 mg/kg weekly and placebo	Placebo
Primary efficacy parameter	Annual change in FEV_1	Decline in FEV_1 and mortality in relation to augmentation therapy	Annual decline in FEV_1	Annual decline in FEV_1	Annual decline in FEV_1	Change in the 15th percentile lung density	$AUC_{0-7\ days}$ postdose	$AUC_{0-7\ days}$, C_{max}, elimination rate, $t_{1/2}$, t_{max}, C_{trough}	Change in the 15th percentile lung density	Change in the 15th percentile lung density
Secondary efficacy parameter	Annual change in FEV_1 by gender, follow-up time, and initial FEV_1% pred	N/A	N/A	15th percentile point of the lung density distribution of the whole lung measured by CT scanning	N/A	Lung function, frequency of exacerbations, and health status St. George's Respiratory Questionnaire	C_{max}, t_{max}, C_{trough}	N/A	Severe COPD exacerbations, basal lung CT densitometry	Spirometry, KCO, shuttle walk

Study findings	Slower decline in FEV_1 in treated vs untreated group ($p = 0.02$) No difference when stratified by gender ($p = 0.64$) or follow-up ($p = 0.46$). Slower FEV_1 pred decline in pts with FEV_1% pred 31—65%	Slower decline in FEV_1 in treated patients with moderately decreased lung function ($p = 0.03$); Decreased mortality in patients receiving therapy ($p = 0.02$)	The rate of decline in FEV_1 in these treated patients (~57 mL/y) was approximately half that reported (historical data) for untreated controls	No difference in FEV_1. Reduced decline of lung tissue ($p = 0.07$)	Slower decline in FEV_1 during treatment period vs pretreatment period for entire group ($p = 0.019$)	CT more sensitive measure of emphysema-modifying therapy than physiology and health status, and demonstrates a trend of Prolastin-C treatment benefit	PK paramaters of Prolastin-C are equivalent to Prolastin	Prolastin-C (120 mg/kg) weekly was well tolerated and provided more physiologic $alpha_1$-PI levels than Prolastin-C (60 mg/kg)	N/A	34% reduction in lung density decline in patients receiving $alpha_1$-PI 60 mg/kg IV compared with placebo. Secondary outcome measures were not statistically significant between treatment groups

AATD $alpha_1$-antitrypsin deficiency, *AE* adverse event, *$Alpha_1$-PI* $alpha_1$-proteinase inhibitor, *AUC* area under the curve, *ChAMP* Comparability pharmacokinetics of Alpha-1 Modified Process, C_{max} maximum plasma concentration, C_{trough} lowest concentration prior to administration of next dose, *CT* computed tomography, *EXACTLE* Alpha-1-Antitrypsin (AAT) To Treat Emphysema In AAT-Deficient Patients, *FEV_1* forced expiratory volume in 1 s, *KCO* Association of the transfer coefficient, *N/A* not applicable, *NHLBI* National Heart, Lung, and Blood Institute, *PK* pharmacokinetics, *Pred* predicted, *SPARK* Safety and Pharmacokinetics of Alpha-1 proteinase Inhibitor in Subjects With Alpha1-Antitrypsin Deficiency, *SPARTA* Study of ProlAstin-c Randomized Therapy with Alpha-1 augmentation, $t_{1/2}$ half-life, t_{max} time to maximum plasma concentration.

PI product. The current standard dose was determined based on the fact that a dose of 60 mg/kg weekly maintained serum levels above the putative protective threshold of 11 uM [10]. However, since this serum level is still below the normal range of alpha$_1$-PI serum levels in healthy patients (20—53 uM) [6], there has been an interest in evaluating the efficacy of higher doses of alpha$_1$-PI. Therefore, the SPARTA study has been designed to include a higher dose of Prolastin-C of 120 mg/kg weekly. Prior to initiating SPARTA, the **S**afety and **PhAR**maco**K**inetic (SPARK) trial, a multicenter, randomized, double-blind, crossover study, was conducted to ensure that the safety and pharmacokinetics (elimination rate constant and $t_{1/2}$) of weekly infusions of Prolastin-C 120 mg/kg were similar compared with the 60 mg/kg weekly dose. The results of SPARK demonstrated that 120 mg/kg Prolastin-C weekly was well tolerated and conferred higher serum levels of alpha$_1$-PI (27.7 uM) compared with 60 mg/kg (17.3 uM) in patients with AATD [27]. SPARTA is a randomized, double-blind, placebo-controlled trial assessing the effects of two separate doses (60 and 120 mg/kg) weekly of Prolastin-C on emphysema progression over three years.

Study design

SPARTA is a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial (protocol number: GTi1201, clinicaltrials.gov identifier: NCT01983241) designed to evaluate two dose regimens (60 and 120 mg/kg) of Prolastin-C versus placebo (0.9% sodium chloride for injection, USP). During the 21-day screening phase, patients will be assessed for study eligibility and will receive a baseline CT scan. At the baseline visit, eligible patients (N = 339) will be randomized 1:1:1 to receive weekly IV infusions of Prolastin-C 60 mg/kg, Prolastin-C 120 mg/kg, or placebo. Randomization will be stratified by the baseline forced expiratory volume in 1 s (FEV_1; 30%—<35%, 35%—60%, and >60%—<80%) with patients in each stratum randomized to one of the three treatments to ensure balanced assignment. Patients will receive weekly treatments according to their assigned treatment group for 156 weeks (treatment phase). Computed tomography scans will be performed at screening (baseline CT scan) and at weeks 52, 104, 130, and 156 of the treatment phase (Fig. 1). Patient participation will conclude after completing the end-of-study visit at week 160. All of the study procedures will be conducted within International Conference on Harmonization Good Clinical Practice guidelines.

Study population

Eligible patients for study inclusion are to be 18—70 years of age, have a documented total alpha$_1$-PI serum level <11 μM, and have a diagnosis of congenital AATD with an allelic combination of *PiZZ*, *PiSZ*, *PiZ*(null), *Pi*(null)(null), *PiS*(null), or at-risk alleles as determined by the medical monitor. To ensure all patients have emphysema, patients must meet one of 2 criteria: 1) have a carbon monoxide diffusing capacity (DLco) ≤60% of the predicted value (corrected for hemoglobin) within the previous two years; or 2) show evidence of emphysema on CT scan within the previous two years per the investigator's judgment. This criterion in combination with the required FEV_1 of ≥30% and <80% of predicted and a reduced serum level of AAT along with a documented deficiency allelic combination will ensure a study population with obstructive lung disease. The inclusion and exclusion criteria are listed in Table 2.

Treatments

Patients included in the study will receive a total of 156 blinded IV infusions of Prolastin-C (60 mg/kg or 120 mg/kg) or placebo, administered on a weekly schedule. Infusions will be conducted at investigators' study sites, ambulatory

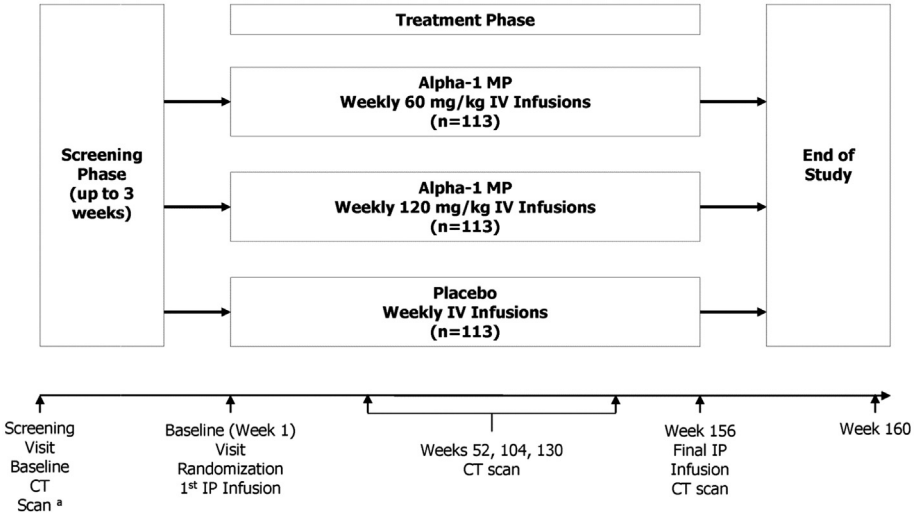

Figure 1 Study design. *CT* computed tomography, *IP* investigational product, *IV* intravenous *MP* modified protein. [a]Can be performed anytime during the screening phase but must be completed, reviewed, and approved by the central CT vendor prior to the baseline (week 1) visit.

Table 2 SPARTA key inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
1. Documented total alpha$_1$-PI serum level <11 μM	1. Has received alpha$_1$-PI augmentation therapy for >1 month within the 6 months prior to screening
2. Diagnosis of congenital AATD with an allelic combination of *PiZZ*, *PiSZ*, *PiZ*(null), *Pi*(null)(null), *PiS*(null), or at-risk alleles[a]	2. Has received alpha$_1$-PI augmentation therapy within 1 month of screening
3. At screening week 3, a postbronchodilator FEV$_1$ $\geq$30% and $<$80% of the predicted value and a FEV$_1$/forced vital capacity $<$70% (Global Initiative for Chronic Obstructive Lung Disease stage 2 or 3) [29]	3. Has experienced a COPD exacerbation within the 5 weeks prior to screening or during the screening phase[b]
4. $DL_{CO} \leq$ 60% of the predicted value (corrected for HgB) within the past 2 years or evidence of emphysema on the CT scan within the past 2 years based on the judgment of the investigator	4. Unable to physically (eg, unable to fit inside the CT scanner) or mentally (eg, claustrophobic) undergo a CT scan
5. Clinical evidence of emphysema per the investigator's judgment	5. A history of lung or liver transplant
	6. Any lung surgery during the prior 2 years (excluding lung biopsy)
	7. On the waiting list for lung surgery, including lung transplant
	8. Smoking during the past 12 months or a positive urine cotinine test at screening due to smoking
	9. History of anaphylaxis or severe systemic response to any plasma-derived alpha$_1$-PI preparation or other blood product(s)
	10. Use of systemic steroids above a stable dose equivalent to 5 mg/day prednisone within the 5 weeks prior to screening or during the screening phase[c,d]
	11. Use of systemic or aerosolized antibiotics for a COPD exacerbation within the 5 weeks prior to screening or during the screening phase[d]
	12. Known selective or severe immunoglobulin A deficiency

AATD alpha$_1$-antitrypsin deficiency, *BMI* body mass index, *CT* computed tomography, *DL_{CO}* carbon monoxide diffusing capacity, *HgB* hemoglobin.

[a] Patients with at-risk alleles will be evaluated individually by the medical monitor. In cases of no documented genotype, genotyping (allelic discrimination) and phenotyping will be performed at the time of screening (week -3).

[b] In cases of a patient who has had a COPD exacerbation more than 5 weeks prior to screening but is otherwise appropriate for study participation, investigator discretion should be followed.

[c] Inhaled steroids are not considered systemic steroids; it is recommended that the same dose be maintained throughout the study.

[d] Patients were excluded because administration was indicative of a recent COPD exacerbation.

infusion centers, local healthcare professionals' sites, or a home location via a local healthcare professional or agency. Each week, an unblinded pharmacist or designee will prepare two blinded IV bags (infusion bag 1 and infusion bag 2) to account for the difference in volume between the 60 mg/kg and the 120 mg/kg doses (Fig. 2). Blinding of the three treatment groups will be guaranteed by ensuring all patients receive the same total volume for all treatment groups with no visible differences in external aspects of the treatment groups. Patients who miss 10 or more infusions in a year or more than four consecutive weekly infusions will be considered noncompliant and will be withdrawn from the study.

Use of any other alpha$_1$-PI augmentation therapy or any investigational product will not be permitted during the conduct of the study.

Efficacy variables

The primary efficacy variable is the change from baseline in whole-lung 15th percentile lung density (PD15) at total lung capacity (TLC) using CT densitometry. Whole-lung CT scans will be performed by technicians who have undergone certification by a central CT vendor. The CT scan data obtained at each study site will be sent to the central CT vendor for review and analysis in a blinded manner, and this data will be used to evaluate efficacy. It is required that the baseline CT scan obtained during the screening phase be

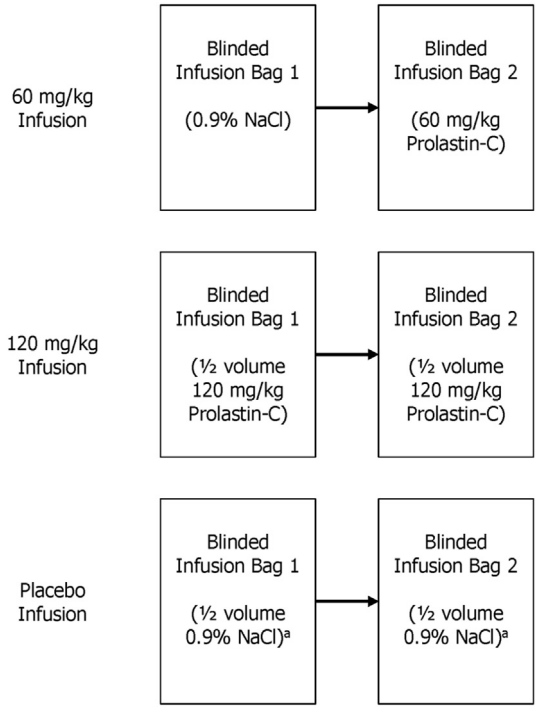

Figure 2 Infusion bag blinding. [a]The total placebo (0.9% Sodium Chloride for Injection) volume will be calculated based on the 120 mg/kg dose.

completed, reviewed, and approved by the central CT vendor prior to the baseline visit to ensure the patients have emphysema, according to the inclusion criteria. The CT scans conducted during the treatment phase should be performed within ±30 days of the scheduled CT visit. Within 15 min to 4 h prior to performing each CT scan, each patient will be administered an inhaled, short-acting bronchodilator (eg, albuterol). Each patient should have all protocol-specified CT scans performed using a same scanner during the study.

Secondary efficacy variables include the incidence of severe COPD exacerbations as defined by American Thoracic Society (ATS)/European Respiratory Society (ERS) [30][1] criteria and basal lung CT densitometry (PD15). Exploratory variables will be the following: incidence and severity of COPD exacerbations as defined by ATS/ERS criteria, change from baseline in FEV_1, health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), and assessment of other CT scan parameters (to be determined upon study completion).

Safety variables

Adverse events (AEs) and concomitant medication use will be assessed during the study from screening through week 160/early discontinuation visit. The safety variables evaluated will be adverse events (AEs), serious AEs (SAEs), and discontinuations due to AEs and SAEs. Physical examinations (complete and respiratory) will be conducted, and clinical laboratory parameters, including determination of high-sensitivity C-reactive protein and Prolastin-C immunogenicity, will also be assessed. For immunogenicity testing, blood samples drawn at baseline, week 13, and week 52 will be assayed for antibodies against Prolastin-C. Samples with a positive test result based on both screening and confirmatory assays will subsequently be tested for neutralizing antibodies and the antibody titer. Patients will be withdrawn from the study if they experience a decline in FEV_1 at a rate of ≥134.4 mL/year at or after week 104.

Follow-up

Any patients who receive investigational product and discontinue early from the study will be requested to return for early discontinuation visit procedures as close as possible to 28 days after their last treatment administration. In addition, all patients who complete all three years of the SPARTA trial as well as those patients who are withdrawn specifically due to meeting the FEV_1 rate decline will be eligible to enroll into a subsequent two-year, open-label study.

[1] **Mild**: involves an increase in one or more respiratory symptoms (dyspnea, cough, and/or sputum) that is controlled by the subject with an increase in the usual medication. **Moderate**: requires treatment with systemic steroids and/or antibiotics. **Severe**: describes exacerbations that require hospitalization (Note: For the purpose of this protocol, an emergency department stay >24 h is considered a hospitalization).

Statistical considerations

Study populations

Efficacy analyses will be performed on the intent-to-treat (ITT) population, which will consist of all patients who are randomized. The primary efficacy analyses of the CT scan data will be based on the modified ITT (mITT) population, which will consist of all patients in the ITT population with a valid baseline and at least 1 valid postbaseline CT scan measurement. The safety population will comprise all randomized patients who receive at least 1 infusion of study treatment. The per-protocol population will consist of all randomized patients who fulfill all entry criteria, have ≥80% treatment compliance, a valid baseline CT scan and ≥1 valid postbaseline CT assessment, and a randomization code that was not broken by the investigator.

Efficacy analyses

For the primary efficacy analysis, a random coefficient regression model will be used to compare the 60 mg/kg or 120 mg/kg dose of Prolastin-C to placebo. The model will include TLC-adjusted lung density as the dependent variable and treatment, center/region, and treatment-by-time interaction as fixed effects and intercept and time as random effects. The Hochberg procedure will be used to control the experiment-wise alpha level at 0.05. As a sensitivity analysis, change from baseline of the TLC-adjusted lung density to endpoint will be analyzed using analysis of covariance (ANCOVA) for the comparison of the two active treatment groups vs placebo. Other efficacy variables will be analyzed by a random coefficient regression model and ANCOVA for PD15 of basal lung region using CT densitometry, other CT scan parameters, FEV_1, and SGRQ. The incidence of exacerbations will be analyzed using a Poisson regression model with treatment and center/region as fixed effects and the duration in the study as an offset variable. The annual COPD exacerbation rates will also be analyzed using analysis of variance (ANOVA) with treatment and center/region as fixed effects.

Safety analysis

The documented AEs, SAEs, drug-related AEs, AEs by severity, and laboratory tests will be summarized using descriptive statistics. Deaths, SAEs, and AEs leading to premature discontinuation from the study will be listed. For all laboratory tests, the original value and the change from baseline will be summarized for numeric results and the frequency/percentage will be summarized for qualitative results. The results of physical/respiratory examinations will also be presented.

Determination of sample size

The number of patients needed in each treatment arm was estimated based on Schluchter et al. [21], together with simulations using data from the Alpha-1-Antitrypsin (AAT) To Treat Emphysema In AAT-Deficient Patients (EXACTLE)

trial [23]. Based on the change from baseline PD15 as the primary endpoint analyzed using ANCOVA for a 3-year trial, it was determined that 75 patients per arm would achieve at least 80% power for an alpha level of 0.05 with a treatment effect size of 0.7 g/L per year with between-subject variation of 0.6 g/L and within-patient variation of 2.3 g/L. For multiplicity adjustment using the Hochberg procedure, 90 patients per arm will be needed to achieve 80% power for an alpha level of 0.025. Based on 90 patients per arm and considering a 20% dropout rate, the enrollment goal for SPARTA is 113 patients in each arm.

Discussion

Optimization of the treatment of patients with AATD has been hindered by difficulties associated with a disease that is relatively uncommon, thus there is a limited number of patients available for study purposes. Furthermore, there is uncertainty regarding the most appropriate clinical outcome measure of emphysema progression in clinical trials. FEV_1 is the "gold standard" clinical measure of COPD progression [23]. Although measurement of FEV_1 is easy to perform and well established, study estimates indicate that the detection of differences in FEV_1 decline over a 3-to-5-year period would require a large number of patients due to the slow progression of AATD. In addition, FEV_1 does not provide information about lung tissue loss, but about the resultant change in lung function [30]. DLco has also been used extensively to evaluate COPD progression, however, there is a lack of uniformity in its assessment of disease progression across the spectrum of disease severity [31]. Chronic obstructive pulmonary disease exacerbations are important clinical manifestations of COPD due to AATD and they are frequently evaluated in clinical trials. However, they are subjective and there is no validated tool to allow a standardized method of defining the start and end of an exacerbation or the severity of the exacerbation [31]. Thus, long-term trials that incorporate sensitive and objective measures of changes in lung structure are needed to evaluate the efficacy of $alpha_1$-PI augmentation therapy in patients with AATD.

Computed tomography scan densitometry has been shown to be a sensitive measure of changes in the architecture of the lung. Dirksen et al., published results supporting the use of CT scans for lung density measurements in patients with AATD [25]. Subsequently, the EXACTLE (ClinicalTrials.gov Identifier NCT00263887) trial, a two-year, multicenter, randomized, exploratory trial, was conducted to assess the frequency of exacerbations and the progression of emphysema using multislice CT scans in patients with AATD receiving Prolastin 60 mg/kg. The results of EXACTLE showed that CT is a more sensitive outcome measure of emphysema-modifying therapy than physiology and health status and demonstrated a trend toward a treatment benefit of augmentation therapy [23]. The multinational, **R**andomized, placebo-controlled trial in **A**lpha-1 **P**roteinase **I**nhibitor **D**eficiency (RAPID) used CT densitometry to evaluate the effects of the $alpha_1$-PI Zemaira® (CSL Behring, King of Prussia, PA) on the progression of lung tissue loss over two years. Investigators reported a 34% reduction in lung density decline evaluated by PD15 at TLC in patients receiving $alpha_1$-PI 60 mg/kg IV compared with placebo. These results suggest that $alpha_1$-PI augmentation therapy can reduce lung tissue decline, and provide additional evidence that CT densitometry can effectively measure lung tissue loss in patients with emphysema [23]. However, CT densitometry is a relatively recent entrant into the study of COPD progression and clinicians may lack familiarity, which could complicate study interpretation [22]. Increased use of CT densitometry in clinical trials as well as the clinical setting could overcome this barrier.

The results of the SPARK study, which provided the PK and safety rationale for evaluating a higher dose, demonstrated that an increased weekly dose of 120 mg/kg Prolastin-C in patients with AATD was well tolerated and safe. This higher dose resulted in a mean steady state trough of $alpha_1$-PI (27.7 μM), which is within the normal range of $alpha_1$-PI serum levels in healthy patients (20—53 μM). In contrast, the standard dose of 60 mg/kg Prolastin-C weekly provided a mean steady state trough of 17.3 μM, consistent with serum levels of $alpha_1$-PI that are greater than the protective threshold of 11 μM but still lower than the levels of individuals without AATD with normal serum $alpha_1$-PI levels [27]. The achievement of nondeficient levels of $alpha_1$-PI may decelerate the rate of lung tissue damage that occurs in patients with AATD, thus reducing the lung function decline and improving patient quality of life. The results of SPARK provided the basis for the dose regimens selected for the SPARTA trial.

Conclusions

In comparison with previous clinical trials investigating the treatment of patients with AATD, SPARTA is distinguished by a number of important features. The SPARTA trial is placebo-controlled and incorporates two doses of Prolastin-C administered weekly (60 mg/kg or 120 mg/kg). These two dose regimens of Prolastin-C will be administered to enrolled patients for a duration of three years, which exceeds by at least one year the study periods used in previous trials examining the effects of $alpha_1$-PI administration. Furthermore, the established outcome assessments of pulmonary function based on lung architecture will be evaluated by a CT scan at total lung capacity as well as a basal CT scan to evaluate the lower lobes of the lung, which are typically affected by AATD-associated emphysema. Pulmonary function will also be assessed by spirometry measures performed at a central laboratory. Collectively, these features of SPARTA are anticipated to provide much-needed, robust results to demonstrate the efficacy of Prolastin-C augmentation therapy in patients with AATD.

The results of SPARTA are intended to provide data demonstrating a slowed progression of emphysematous lung disease in patients with AATD receiving weekly infusions of Prolastin-C augmentation therapy. This study will also assess whether there is incremental clinical benefit from a dose (120 mg/kg) that increases $alpha_1$-PI levels to within the normal range of healthy individuals. Furthermore, these results are anticipated to help underscore the

importance of augmentation therapy in the treatment of patients suffering from this condition.

Conflict of interest

Sandra Camprubi and Jaume Ayguasanosa are employed by Instituto Grifols S.A. (Sant Cugat del Vallés, Barcelona, Spain); Rhonda Griffin, Junliang Chen, and Susan Sorrells are employed by Grifols Inc. (Research Triangle Park, NC, USA). Conduct of research was funded by Grifols Inc.

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