CLINICAL STUDY PROTOCOL

PRODUCT: ARALAST NP and GLASSIA

STUDY TITLE: A Stage 1, Prospective, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Alpha$_1$-Proteinase Inhibitor (A1PI) Augmentation Therapy in Subjects with A1PI Deficiency and Chronic Obstructive Pulmonary Disease (COPD)

STUDY SHORT TITLE: Stage 1 Study of ARALAST NP and GLASSIA in A1PI Deficiency

PROTOCOL IDENTIFIER: 460503

CLINICAL STUDY PHASE 3/4

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Study Sponsor(s):

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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

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1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs MUST BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR TO MEET THE 24 HOUR TIMELINE REQUIREMENT

See SAE Protocol Sections for further information and SAER form for contact information.
Further details are also available in the study team roster.

For definitions and information on the assessment of these events, refer to the following:

- Adverse events (AE), Section 12.1
- SAE, Section 12.1.1.1
- Assessment of AEs, Section 12.1.2

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	ARALAST NP, GLASSIA
Name(s) of Active Ingredient(s)	Alpha$_1$-Proteinase Inhibitor (Human)
CLINICAL CONDITION(S)/INDICATION(S)	
• Clinically evident emphysema due to severe congenital deficiency of alpha$_1$-proteinase inhibitor (A1PI), also known as alpha$_1$-antitrypsin (AAT) deficiency	
PROTOCOL ID	460503
PROTOCOL TITLE	A Stage 1, Prospective, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Alpha$_1$-Proteinase Inhibitor (A1PI) Augmentation Therapy in Subjects with A1PI Deficiency and Chronic Obstructive Pulmonary Disease (COPD)
Short Title	Stage 1 Study of ARALAST NP and GLASSIA in A1PI Deficiency
STUDY PHASE	Ph 3/4 depending on market authorization status per country
PLANNED STUDY PERIOD	
Initiation	Q1 2016
Primary Completion	Q1 2020
Study Completion	Q1 2020
Duration	Approximately 4.2 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• To conduct a pilot study to evaluate the safety and efficacy of weekly administration of A1PI augmentation therapy in subjects with A1PI deficiency and emphysema / COPD.	
Primary Objective	
1. To evaluate the effect of weekly A1PI augmentation therapy on the rate of change in lung density assessed by computerized tomography (CT) lung densitometry, based on pooled data across dose levels for each of the A1PI products.	
Secondary Objective(s)	
Efficacy: To examine the relationship between A1PI dose (60 mg/kg body weight [BW]/week and 120 mg/kg BW/week) and the rate of change in lung density assessed by CT for each of the A1PI products. **Safety:** • To assess the safety and tolerability of ARALAST NP and GLASSIA augmentation therapy at doses of 60 and 120 mg/kg BW/week. To monitor the formation of anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA. **Pharmacokinetics:** • To examine the relationship between A1PI dose and steady-state trough plasma A1PI levels following weekly administration of ARALAST NP or GLASSIA.	

Exploratory Objectives	
[redacted]	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy, Safety, Pharmacokinetic (PK)
Control Type	Concurrent (Placebo)
Study Indication Type	Treatment
Intervention model	Factorial
Blinding/Masking	Double-Blind
Study Design	This is a Phase 3/4, prospective, randomized, placebo-controlled, double-blind, multi-center pilot study to evaluate the safety and efficacy of weekly administration of ARALAST NP and GLASSIA augmentation therapy in subjects with A1PI deficiency and emphysema / COPD using a dose of 60 mg/kg BW/week (dose currently-approved by the Food and Drug Administration (FDA)), and a higher, exploratory dose (120 mg/kg BW/week) versus placebo. Approximately 138 adult subjects diagnosed with severe congenital A1PI deficiency and emphysema / COPD will be enrolled to meet the target of 110 randomized subjects, assuming a 20% screen failure rate. Subjects may be either A1PI naïve (untreated), previously treated, or currently receiving A1PI augmentation therapy at the time of study entry. Subjects who are receiving or have been treated within 4 weeks of screening, with A1PI augmentation therapy will be required to have their pre-study A1PI augmentation therapy discontinued and undergo a washout period of at least 4 weeks in order for A1PI levels to return to endogenous (pre-augmentation) levels. Plasma A1PI levels will be assessed to verify adequacy of A1PI washout and to confirm diagnosis of A1PI deficiency. All other screening procedures may be performed prior to the completion of the washout period. After signing the informed consent, subjects will be screened for eligibility. Subjects meeting eligibility criteria will undergo baseline assessments prior to the first dose of investigational

	product (IP). Subjects will be randomly assigned in a 1:1:1:1:1.5 ratio to receive one of the following five treatments for 24 months (104 weeks): Group 1: ARALAST NP 60 mg/kg BW/week (20 subjects) Group 2: ARALAST NP 120 mg/kg BW/week (20 subjects) Group 3: GLASSIA 60 mg/kg BW/week (20 subjects) Group 4: GLASSIA 120 mg/kg BW/week (20 subjects) Group 5: Placebo (Human albumin 2% in normal saline) 6 mL/kg BW/week (30 subjects) IP will be administered via weekly IV infusions. To maintain blinding, all subjects will receive IP in two identical intravenous (IV) bags that are opaque or covered with opaque overwraps. Subjects in Group 1 and Group 3 will receive one IV bag of active IP and one IV bag of volume-matched placebo solution (human albumin 2% in normal saline). Subjects in Group 2 and Group 4 will receive two identical IV bags of active IP. Subjects in Group 5 will receive two identical IV bags of placebo solution (human albumin 2% in normal saline). The first IP infusion will be administered at the study site to monitor for safety and tolerability. At the investigator's discretion, subsequent infusions may be administered at the study site or at another suitable location (eg, the subject's home) by a qualified healthcare professional, except for those that occur during the same week as the clinic visits (see Table 20-1, footnote k). Study visits will occur according to the schedule of events for clinical and laboratory assessments. Clinical and/or laboratory assessments, as appropriate, will be postponed in the event of a moderate or severe lower respiratory tract infection (LRTI)/acute pulmonary exacerbation (APE) until clinical resolution of the LRTI/APE (ie, clinical signs or symptoms are no longer evident) and subject remains stable for at least 4 weeks (or 90 days in the case of a CT assessment) after the end of the LRTI/APE. If a moderate or severe episode of LRTI/APE occurs during the treatment phase, the subject should continue with the planned study visits and receive weekly infusions of IP as planned, unless deemed medically inappropriate by the investigator. All pulmonary exacerbations, adverse events (AEs), and concomitant medications and/or non-drug therapies will be recorded during infusion visits. Upon completion of the treatment period, subjects will be followed for an additional 1 week (± 2 days) for safety monitoring and anti-A1PI antibody assessments.

Planned Duration of Subject Participation	Each subject is expected to participate in the study for a total of 26 months, including: • Screening period up to 6 weeks, • Treatment period of 24 months (104 weeks), and • Post-treatment follow-up period of 1 week (± 2 days)
Primary Outcome Measure	
• Rate of change in lung density (15th percentile of the lung density measurements [PD15] as assessed by CT densitometry), based on Group 1 and Group 2 (ARALAST NP) versus placebo, and Group 3 and Group 4 (GLASSIA) versus placebo	
Secondary Outcome Measure(s)	
Efficacy • Rate of change in lung density (as assessed by CT) for each treatment group **Pharmacokinetics** • Mean steady state trough concentration of antigenic and functional A1PI for ARALAST NP and GLASSIA at each dose level **Safety** 1. Number and rate of related and unrelated serious and non-serious AEs 2. Number and rate of temporally related serious and non-serious AEs (ie, AEs which began during or within 72 hours following the end of IP infusion) 3. Number and rate of suspected adverse reactions plus adverse reactions (ARs) 4. Number (proportion) of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped due to AEs 5. Number (proportion) of subjects who develop anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA	
Exploratory Outcome Measure(s)	
[redacted]	

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**ARALAST NP** **Doses:** 60 mg/kg BW/week, 120 mg/kg BW/week **Dosage form**: Injection, powder, lyophilized, for solution **Dosage frequency**: Weekly **Mode of Administration**: Intravenous **GLASSIA** **Doses:** 60 mg/kg BW/week, 120 mg/kg BW/week **Dosage form**: Injection, solution **Dosage frequency**: Weekly **Mode of Administration**: Intravenous
Placebo/ Control/ Comparator	**Human albumin 2%** **Dose:** 6 mL/kg BW/week **Dosage form**: Injection, solution **Dosage frequency**: Weekly **Mode of Administration**: Intravenous
SUBJECT SELECTION	
Targeted Accrual	110 randomized subjects
Number of Groups/Arms/Cohorts	5
Inclusion Criteria	

Subjects who meet ALL of the following criteria are eligible for this study:

- Adults of either gender 18 years of age or older at the time of screening.
- Endogenous plasma A1PI level < 8 µM at any time during the Screening period for treatment-naïve subjects, or following 4-weeks minimum wash-out from previous augmentation therapy in treatment-experienced subjects. The screening plasma A1PI level may be repeated if a subject obtains an exclusionary value that is suspected to be due to inadequate washout of A1PI.

Subject has documented A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, Pi*Null/Null, or other rare genotypes (except PI*MS, PI*MZ, or PI*SZ).

Clinically evident mild-moderate COPD (according to GOLD criteria for diagnosis) at the time of screening defined as follows:

a. FEV_1 is ≥ 30% and ≤ 80% predicted
b. If FEV_1 is > 80% predicted, then FEV_1/forced vital capacity (FVC) must be < 0.7 or DL_{CO} must be ≥ 30% and ≤ 65% predicted

If the subject is treated with any respiratory medications including inhaled bronchodilators, inhaled corticosteroids, or systemic corticosteroids (e.g. prednisone ≤ 10 mg/day or its equivalent), the doses of the subject's medications have remained stable for at least 28 days prior to screening.

No clinically significant abnormalities (other than emphysema, bronchitis or bronchiectasis) detected via a chest computed tomography (CT) or chest X-ray at the time of screening.

If female of childbearing potential, subject must have a negative pregnancy test at screening and agree to employ adequate birth control measures for the duration of the study.

Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for the study:

- Known ongoing or history of clinically significant pulmonary impairment other than emphysema / COPD.

The subject is experiencing lower respiratory infection (LRTI)/acute pulmonary exacerbation (APE) at the time of enrollment (signing ICF). Subject may be re-screened after both clinical resolution of LRTI/APE and having also remained stable for at least 4 weeks after the end of LRTI/APE.

Known ongoing or history of cor pulmonale.

Known resting partial pressure of carbon dioxide ($PaCO_2$) levels of > 45 mmHg.

Clinically significant congestive heart failure with New York Heart Association (NYHA) Class III/IV symptoms.

The subject has received an organ transplant, has undergone major lung surgery, or is currently on a transplant list.

Known history of ongoing malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix).

Smoker or subject that has ceased smoking for less than one year prior to screening whose levels of cotinine are outside of the normal range of a non-smoker. All subjects must agree to refrain from smoking throughout the course of the study.

The subject is receiving long-term therapy (> 28 days) of parenteral corticosteroids or oral corticosteroids at doses greater than 10 mg/day of prednisone or its equivalent.

The subject is receiving long-term round-the-clock oxygen supplementation (other than temporary for acute COPD exacerbation, or supplemental O_2 with continuous positive airway pressure [CPAP], or bi-level positive airway pressure [BiPAP] during the day).

Subject has contraindications for CT (eg, body weight and/or body size exceeding the weight and gantry size limits specified by the manufacturer of the CT scanner, inability to lie flat in the CT scanner, claustrophobia, metal prosthesis or pacemaker in the chest wall or upper extremity that would impact lung density assessment).

Subject is unwilling or unable to modify bronchodilator medications for 6 hours for short acting β2 agonists, 24 hours for long-acting β2 agonists, and 48 hours for long acting anticholinergics prior to the scheduled quantitative CT scan.

Known severe immunoglobulin A (IgA) deficiency (ie, IgA level < 8 mg/dL at screening).

Known history of hypersensitivity following infusions of human blood or blood components (eg, human immunoglobulins or human albumin).

Presence of clinically significant laboratory abnormalities at the screening that meets one or more of the following criteria:

a. Serum alanine aminotransferase (ALT) ≥ 3 times upper limit of normal (ULN)
b. Serum total bilirubin ≥2 times ULN
c. Proteinuria > +2 on dipstick analysis
d. Absolute neutrophil count (ANC) ≤ 1500 cells/mm^3
e. Hemoglobin (Hgb) ≤ 10.0 g/dL
f. Platelet count ≤ 100,000/mm^3
g. Serum creatinine ≥2 times ULN

The subject has a clinically significant medical, psychiatric, or cognitive illness, is a recreational drug/alcohol user, or has any other uncontrolled medical condition (eg, unstable angina, transient ischemic attack, uncontrolled hypertension) that, in the opinion of the investigator, would affect subject's safety or compliance or confound the results of the study.

Subject has been exposed to another IP within 28 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.

Subject is a family member or employee of the investigator.

If female, subject is pregnant or nursing at the time of enrollment.

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size proposed for this study will permit estimates of averages and variances in rates of change in lung density and other parameters after 24 months of treatment in each treatment group and pooled within product. Information from this study may be used in the planning for a larger Stage 2 study. This study will not be powered to permit hypothesis testing of primary or secondary outcome measures.

Planned Statistical Analysis

Primary Statistical Analyses:

Analyses will be performed on the rate of change in lung density as measured by CT densitometry and based on Group 1 and Group 2 (ARALAST NP) versus placebo and Group 3 and Group 4 (GLASSIA) versus placebo using the full analysis set (FAS) (as primary analysis) and the modified FAS and per protocol (PP) analysis sets (as supportive analyses).

Mean rates of change and 95% confidence intervals (CIs) will be estimated within a random coefficients model by pooling data from both dose levels for each A1PI product separately, and they will be compared to the mean rates of change in placebo group (for the primary outcome measure).

Secondary Statistical Analyses:

Secondary Efficacy Endpoints

The same model used for the primary outcome measure will be utilized to obtain estimates of mean rates of change of lung density per dose level per A1PI product. Mean rates of change and 95% CIs will be estimated within this model for each product at each dose level separately, and they will be compared to the mean rates of change in placebo group.

Graphs showing CT lung densities over time will be prepared, data permitting.

Safety

Summaries of AEs will be conducted for each treatment group. AEs occurring during or after IV infusions will be summarized by seriousness, severity, and relatedness to treatment with ARALAST NP, GLASSIA, or placebo. All AEs will be categorized and summarized according to Medical Dictionary for Regulatory Activities (MedDRA) terms.

All analyses of AEs will be based on the safety analysis set.

Untoward medical occurrences prior to the first IP administration will be listed separately.

Changes in chemistry and hematology parameters will be summarized using descriptive statistics and will be presented graphically. The number (proportion) of subjects who experienced clinically significant abnormal laboratory values post-treatment will be summarized for each treatment group. Shift tables will be prepared.

To evaluate immunogenicity of ARALAST NP and GLASSIA after repeated dosing, the incidence of anti-A1PI antibody formation following ARALAST NP and GLASSIA administration will be summarized for each treatment group separately, and pooled across dose levels for each product.

Pharmacokinetics (PK)

Steady state trough concentrations of antigenic and functional A1PI will be summarized per dose per A1PI product.

Exploratory Analyses:

[redacted]

[redacted]

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-minute walk test
A1PI	Alpha1-Proteinase Inhibitor
AE	Adverse event
AAT	Alpha1-antitrypsin
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APE	Acute Pulmonary Exacerbation
AR	Adverse Reaction
AST	Aspartate aminotransferase
ATS	American Thoracic Society
B19V	Parvovirus B19
BMI	Body mass index
BiPAP	bi-level positive airway pressure
BODE	Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index
BUN	Blood urea nitrogen
BW	Body weight
CFR	Code of Federal Regulations
CJD	Creutzfeldt-Jakob disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CT	Computed tomography
dL	Deciliter(s)
DL_{CO}	Diffusing capacity of carbon monoxide
DMC	Data monitoring committee
EC	Ethics Committee
EKG	Electrocardiogram
ERS	European Respiratory Society
FAS	Full analysis set

Abbreviation	Definition
FDA	Food and Drug Administration of the United States
FEV_1	Forced expiratory volume in one second
FEV_1/FVC	Percentage of vital capacity expired in the first second of maximal expiration
FRC	Functional residual capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAV	Hepatitis A virus
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
HEV	Hepatitis E virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hr	Hour
HRQoL	Health-related quality of life
HU	Hounsfield Units
IB	Investigator's Brochure
IC	Inspiratory capacity
ICF	Informed consent form
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Investigational product
IRT	Interactive Response Technology
IV	Intravenous
IWRS	Interactive Web Response System
kD	Kilodaltons
kg	Kilogram
LDH	Lactate dehydrogenase

Abbreviation	Definition
LRTI	Lower respiratory tract infection
µM	Micromolar
µmol/L	Micromoles per liter
MANOVA	Multivariate analysis of variance
MCS	Mental Component Score
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
mg	Milligram
mITT	modified intent-to-treat
MMRC	Modified Medical Research Council
Min	Minute (s)
mL	Milliliter
NE	Neutrophil elastase
NMC	Non-medical complaint
NYHA	New York Heart Association
$PaCO_2$	Partial pressure of carbon dioxide
PCS	Physical Component Score
PFT	Pulmonary function test
PK	Pharmacokinetic
PP	Per-protocol
RBC	Red blood cell
SAE	Serious adverse event
SAER	Serious adverse event report
SAS	Safety analysis set
S/D	Solvent/detergent
SF-36	Short Form (36) Health Survey
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SIC	Subject identification code
TLC	Total lung capacity
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia

Abbreviation	Definition
WBC	White blood cell
wk	Week

6. BACKGROUND INFORMATION

Alpha1-Proteinase Inhibitor (A1PI), also known as alpha1-antitrypsin (AAT), is a serum glycoprotein of molecular mass 52 kilodaltons (kD).[1] The protein is synthesized in the liver and is reported to be present in serum at levels between 20 and 53 µM (104 to 275.6 mg/dL).[2]

Severe A1PI deficiency (also known as AAT deficiency) is an autosomal recessive hereditary disorder affecting an estimated 34,395 to 48,904 individuals in the United States (US), with 91.6% being Caucasian Americans, 7.8% Hispanic Americans, and 0.5% African Americans.[3;4] Individuals with severe deficiency are defined as those with serum A1PI levels less than 35% of the average normal level[5;6], or less than 11 µM.[7-9] In addition, genetic variants associated with reduced A1PI levels also produce an altered form of A1PI, the capacity of which to inhibit neutrophil elastase (NE) is reduced (as shown in Table 6-1).[10] Severely affected (Pi*Null/Null) individuals have no detectable A1PI protein in their serum.

Table 6-1
Serum Levels of A1PI in Various Genotypes

A1PI Units	Genotype					
	Pi*MM	**Pi*MZ**	**Pi*SS**	**Pi*SZ**	**Pi*ZZ**	**Pi*Null/Null**
µM	20-48	17-33	15-33	8-19	2.5-7	Not detectable
mg/dL	150-350	90-120	100-200	75-120	20-45	

Modified from American Thoracic Society (ATS)/European Respiratory Society (ERS) statement on Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency.

A1PI deficiency increases the risk for development of panacinar emphysema.[1;11] The threshold level of A1PI in the lower respiratory tract needed to provide clinical benefit is unknown, however, emphysema may develop because the level of A1PI in the lower respiratory tract is insufficient to inhibit serine proteases. Serine proteases, such as NE, are present in the lower respiratory tract in higher than normal concentrations as a result of inflammation or infection.[12] If left unchecked, due to insufficient A1PI, the proteolytic activity of these proteases can destroy the connective tissue framework of the lung parenchyma.[13;14]

Therapy for A1PI-deficient subjects is aimed towards replacement or augmentation of serum A1PI levels.[1;7;9;12;14-19] This therapy is based upon the concept that, if the serum level of A1PI is increased, it will lead to higher A1PI concentrations in the lung parenchyma, which in turn, may mitigate the A1PI protease imbalance, thereby preventing or slowing the destruction of lung tissue and thus the clinical course of the disease.[7;12]

Wewers et al. demonstrated that at steady-state, augmentation therapy with once a week dosing of A1PI, at a dose level of 60 mg/kg BW/week, in subjects with A1PI deficiency and emphysema and of Pi*Z/Z genotype resulted in trough levels > 11 μM.[19] Historically, it was believed that 11μM is the protective threshold level, based on the assumption that A1PI deficient (severe) subjects with genotypes Pi*Z/Z, Pi*Null/Null or Pi*Z/Null had A1PI levels below 11 μM had emphysema, while the Pi*S/Z subjects, who at that time were considered to have an average A1PI level of 11 μM, were protected from emphysema. However, recent data indicate that the 11μM threshold assumption may not be valid and higher doses of A1PI may need to be evaluated.

The primary purpose of this study is to assess the safety and efficacy of intravenous ARALAST NP and GLASSIA augmentation therapy administered as an IV infusion at 60 mg/kg body weight (BW)/week or 120 mg/kg BW/week as compared to placebo. The protective effects of ARALAST NP and GLASSIA are expected to be reflected in the preservation of lung parenchyma, as measured by CT densitometry. In addition, the functional integrity of lung parenchyma will be evaluated by measurements of selected respiratory physiology variables.

The results of this study, along with available scientific data, will be used to design an adequately powered Stage 2 clinical study. The Stage 2 clinical study will be a statistically fully-powered efficacy study for augmentation with A1PI.

6.1 Description of Investigational Product

6.1.1 ARALAST NP

ARALAST NP is approved by the FDA for chronic augmentation therapy in adults with clinically evident emphysema due to severe congenital deficiency of A1PI. ARALAST NP is a sterile, lyophilized preparation of purified human A1PI prepared from large pools of human plasma using the cold ethanol fractionation process, followed by purification steps including polyethylene glycol and zinc chloride precipitations, and ion exchange chromatography.

When reconstituted as directed, the concentration of A1PI is ≥ 16 mg/mL and the specific activity is ≥ 0.55 mg active A1PI /mg total protein. The formulation contains no preservative. The pH of the reconstituted product ranges from 7.2 to 7.8. The reconstituted product is a colorless or slightly yellowish-green solution and be essentially free of visible particles.

Further information can be found in Section 8.7 and in the ARALAST NP prescribing information or in the Investigator's Brochure (IB).

6.1.2 GLASSIA

GLASSIA is approved by the FDA for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of A1PI.

GLASSIA is a sterile, ready-to-use, liquid preparation of purified human A1PI. The solution contains 2% active A1PI in a phosphate-buffered saline solution. The A1PI is prepared from human plasma obtained from US-licensed plasma collection centers using a modified version of the cold ethanol fractionation process then the A1PI is purified using chromatographic methods. The specific activity of GLASSIA is ≥0.7 mg functional A1PI per mg of total protein with ≥90% of the A1PI in the product being monomeric form. The product is clear and colorless to yellow-green and may contain a few protein particles.

Further information can be found in Section 8.7 and in the GLASSIA prescribing information or in the Investigator's Brochure (IB).

6.1.3 Placebo

Human albumin will be used as the placebo control. A low concentration of albumin in normal saline has been selected for use due to its similarity in appearance to ARALAST NP and GLASSIA to help preserve blinding. Human albumin solution will be used to prepare human albumin 2% by appropriate dilution with normal saline solution.

6.2 Clinical Condition/Indication

Clinically evident emphysema or COPD due to severe congenital deficiency of A1PI, also known as AAT deficiency.

6.3 Population to Be Studied

Subjects with emphysema / COPD associated with severe congenital A1PI deficiency with endogenous plasma A1PI level of < 8 µM and documented A1PI genotypes of Pi*Z/Z, Pi*Z/null, Pi*Malton/Z, Pi*Null/Null, or other rare genotypes (except PI*MS, PI*MZ, or PI*SZ).

COPD in this study is defined according to the GOLD criteria for diagnosing mild-moderate COPD as:

- forced expiratory volume in 1 second (FEV_1) 30 to 80% predicted, OR
- FEV_1 predicted > 80% but with $FEV_1/FVC < 0.7$ predicted and diffusing capacity of carbon monoxide (DL_{CO}) of 30 to 65% predicted.

6.4 Findings from Nonclinical and Clinical Studies

Findings from non-clinical and clinical studies for ARALAST NP and GLASSIA are detailed in the respective prescribing information leaflets and/or IB.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

6.5.1 ARALAST NP and GLASSIA

Transmission of blood-borne diseases by administration of ARALAST NP or GLASSIA is a theoretical risk since they are both derived from pooled human plasma. To reduce the potential contamination with blood-borne viruses, stringent procedures have been employed in the manufacture of the product from the screening of plasma donors through plasma collection and preparation. To further improve the margin of safety, the manufacturing process includes treatment with a solvent/detergent (S/D) mixture [tri-n-butyl phosphate and polysorbate 80] to inactivate enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). In addition, a nanofiltration step is incorporated into the manufacturing process to reduce the risk of transmission of enveloped and non-enveloped viruses (such as hepatitis A virus [HAV]). *In vitro* virus clearance studies for both products demonstrated a virus log reduction of 4 or greater.

ARALAST NP and GLASSIA are contraindicated in subjects with antibodies against Immunoglobulin A (IgA) due to risk of severe hypersensitivity. ARALAST NP and GLASSIA may contain trace amounts of IgA. Subjects with known antibodies to IgA, which can be present in subjects with selective or severe IgA deficiency, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, THE INFUSION SHOULD BE DISCONTINUED IMMEDIATELY. Epinephrine and other appropriate supportive therapy should be available for the treatment of any acute anaphylactic or anaphylactoid reaction.

For more specific information regarding the known and potential risks, refer to the ARALAST NP and GLASSIA prescribing information leaflets and/or the respective IB.

While the currently approved dose of 60 mg/kg BW/week is designed to achieve a steady-state plasma A1PI trough concentration of approximately 11 µM, it falls below the low normal value of 20 µM. It is expected that a dose of 120 mg/kg BW/week would result in steady-state trough concentrations of approximately 20 µM and may provide better therapeutic benefit.

Two studies have indicated that A1PI augmentation therapy may be effective in reducing the loss of lung density in severe A1PI deficient subjects. In a randomized study (2 centers, n=56) conducted by Dirksen et al. (1999)[20], A1PI deficient patients received either A1PI treatment at 250 mg/kg BW or albumin at 625 mg/kg BW every 4 weeks for 3 years. The A1PI augmentation therapy appeared to be effective in decreasing the loss of lung tissue measured by CT (although not statistically significant; p=0.07), despite the trough levels falling below the threshold level of 11 µM for several days prior to the next dose. In another placebo-controlled study (EXACTLE Study, 2008 ATS), Dirksen et al. showed a decrease in the loss of lung tissue (p = 0.049 to 0.084, based on the prespecified method of statistical analysis) in 71 subjects treated with A1PI at 60 mg/kg BW/week over a period of 2 to 2.5 years.[21]

6.5.2 Placebo

The placebo contains human albumin in normal saline solution. The volume of the placebo solution, like the volume of ARALAST or GLASSIA, may affect subjects with congestive heart failure (New York Heart Association [NYHA] class III/IV), advanced kidney disease and progressive liver disease.

Albumin is made from human plasma. The theoretical risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, and by testing them for the presence of specific currently active virus infections, as well as by inactivating and/or removing certain viruses from the product. No cases of transmission of viral diseases or prion diseases (e.g. Creutzfeldt-Jakob disease (CJD)) have ever been identified for albumin.

Albumin is contraindicated in subjects with a history of allergic (anaphylactic) reactions to albumin, in severely anemic subjects, and in subjects with cardiac failure.

Serious adverse events (SAEs) following albumin administration are rare.[22] Rarely, infusions of albumin have been associated with nausea, fever, chills or urticaria. Such symptoms usually disappear when the infusion is slowed or stopped for a short period of time.[23-25]

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Conference on Harmonization Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives 2001/20/EC and 2005/28/EC, and applicable national and local regulatory requirements for good pharmacovigilance practices.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

- To conduct a pilot study to evaluate the safety and efficacy of weekly administration of A1PI augmentation therapy in subjects with A1PI deficiency and emphysema / COPD.

7.2 Primary Objective

- To evaluate the effect of weekly A1PI augmentation therapy on the rate of change in lung density assessed by CT densitometry, based on pooled data across dose levels for each of the A1PI products.

7.3 Secondary Objectives

7.3.1 Efficacy

- To examine the relationship between A1PI dose (60 mg/kg body weight [BW]/week and 120 mg/kg BW/week) and the rate of change in lung density assessed by CT densitometry for each of the A1PI products.

7.3.2 Safety

- To assess the safety and tolerability of ARALAST NP and GLASSIA augmentation therapy at doses of 60 and 120 mg/kg BW/week.
- To monitor the formation of anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA.

7.3.3 Pharmacokinetics

- To examine the relationship between A1PI dose and steady-state trough plasma A1PI levels following weekly administration of ARALAST NP or GLASSIA.

7.4 Exploratory Objectives

[redacted]

[redacted]

8. STUDY DESIGN

8.1 Brief Summary

This is a Phase 3/4, prospective, randomized, placebo-controlled, double-blind, multi-center pilot study to evaluate the safety and efficacy of weekly administration of ARALAST NP and GLASSIA augmentation therapy in subjects with A1PI deficiency and emphysema / COPD using a dose of 60 mg/kg BW/week (dose currently-approved by the Food and Drug Administration (FDA)), and a higher, exploratory dose (120 mg/kg BW/week) versus placebo. The results of this trial, along with other available scientific data, may be used to design a statistically-fully-powered (Stage 2) clinical efficacy study of augmentation therapy with A1PI in congenital A1PI deficiency.

8.2 Overall Study Design

Approximately 138 adult subjects diagnosed with severe congenital A1PI deficiency and emphysema / COPD will be enrolled to meet the target of 110 randomized subjects, assuming a 20% screen failure rate. Subjects may be either A1PI naïve (untreated), previously treated, or currently receiving A1PI augmentation therapy at the time of study entry.

Subjects who are receiving or have been treated within 4 weeks of screening, with A1PI augmentation therapy will be required to have their pre-study A1PI augmentation therapy discontinued and undergo a washout period of at least 4 weeks in order for A1PI levels to return to endogenous (pre-augmentation) levels. Plasma A1PI levels will be assessed to verify adequacy of A1PI washout and to confirm diagnosis of A1PI deficiency. All other screening procedures may be performed prior to the completion of the washout period.

After signing the informed consent, subjects will be screened for eligibility. Subjects meeting eligibility criteria will undergo baseline assessments prior to the first dose of investigational product (IP).

Subjects will be randomly assigned in a 1:1:1:1:1.5 ratio to receive one of the following five treatments for 24 months (104 weeks):

Group 1: ARALAST NP 60 mg/kg BW/week (20 subjects)
Group 2: ARALAST NP 120 mg/kg BW/week (20 subjects)
Group 3: GLASSIA 60 mg/kg BW/week (20 subjects)
Group 4: GLASSIA 120 mg/kg BW/week (20 subjects)
Group 5: Placebo (Human albumin 2% in normal saline) 6 mL/kg BW/week (30 subjects)

IP will be administered via weekly IV infusions. To maintain blinding, all subjects will receive IP in two identical IV bags that are opaque or covered with opaque overwraps. Subjects in Group 1 and Group 3 will receive one IV bag of active IP and one IV bag of volume-matched placebo solution (human albumin 2% in normal saline). Subjects in Group 2 and Group 4 will receive two identical IV bags of active IP. Subjects in Group 5 will receive two identical IV bags of placebo solution (human albumin 2% in normal saline). The first IP infusion will be administered at the study site. At the investigator's discretion, subsequent infusions may be administered at the study site or at another suitable location (eg, the subject's home) by a qualified healthcare professional, except for those that occur during the same week as the clinic visits (see Table 20-1, footnote k).

Study visits will occur according to the schedule of events for clinical and laboratory assessments. Clinical and/or laboratory assessments, as appropriate, will be postponed in the event of a moderate or severe lower respiratory tract infection (LRTI)/acute pulmonary exacerbation (APE) until clinical resolution of the LRTI/APE (ie, clinical signs or symptoms are no longer evident) and subject remains stable for at least 4 weeks (or 90 days in the case of CT assessments) after the end of the LRTI/APE. If a moderate or severe episode of LRTI/APE occurs during the treatment phase, the subject should continue with the planned study visits and receive weekly infusions of IP as planned, unless deemed medically inappropriate by the investigator. All pulmonary exacerbations, AEs, and concomitant medications and/or non-drug therapies will be recorded during infusion visits. Upon completion of the treatment period, subjects will be followed for an additional 1 week (± 2 days) for safety monitoring and anti-A1PI antibody assessments.

8.3 Duration of Study Period(s) and Subject Participation

Each subject is expected to participate in the study for a total of 26 months, including:

- Screening period up to 6 weeks,
- Treatment period of 24 months (104 weeks), and
- Post-treatment follow-up period of 1 week (± 2 days)

8.4 Outcome Measures

8.4.1 Primary Outcome Measure

- Rate of change in lung density (15th percentile of the lung density measurements [PD15] as assessed by CT densitometry), based on Group 1 and Group 2 (ARALAST NP) versus placebo, and Group 3 and Group 4 (GLASSIA) versus placebo

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy

- Rate of change in lung density (as assessed by CT) for each treatment group

8.4.2.2 Pharmacokinetics

- Mean steady state trough concentration of antigenic and functional A1PI for ARALAST NP and GLASSIA at each dose level

8.4.2.3 Safety

1. Number and rate of related and unrelated serious and non-serious AEs
2. Number and rate of temporally related serious and non-serious AEs (ie, AEs which began during or within 72 hours following the end of IP infusion)
3. Number and rate of suspected adverse reactions plus adverse reactions (ARs)
4. Number (proportion) of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped due to AEs
5. Number (proportion) of subjects who develop anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA

8.4.3 Exploratory Outcomes Measures

[redacted]

8.5 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Subjects will be randomly assigned to 1 of five treatment regimens (ARALAST NP at 60 mg/kg/week or 120mg/kg/week, GLASSIA at 60 mg/kg/week or 120 mg/kg/week, or placebo control) at a ratio of 1:1:1:1:1.5.

8.5.1 Unblinding Procedures at Study Sites

Randomization codes will be generated and maintained by an Interactive Response System (IRS). Treatment assignment will be blinded to the subject, investigators, study site personnel and the sponsor. Individual study personnel may be unblinded if necessary (e.g. to prepare the infusions or monitor the study source documents).

The randomization assignment is not to be revealed before the study is terminated, except in emergency cases when unblinding is necessary for the clinical management of an SAE. In such events, every attempt must be made to inform the sponsor before breaking the blind or immediately when unblinding has been performed. The investigator may request for the treatment assignment of the specific individual subject involved in the emergency event via the centralized randomization service or the unblinded biostatistician.

8.6 Study Stopping Rules

There are no specific stopping rules for this study; however, the study may be terminated by the sponsor at any time. Additionally, a Data Monitoring Committee (DMC) will be established to monitor the study for any safety or medical concerns, and may recommend stopping the study based on the criteria defined in the DMC charter (see Section 16.4).

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 ARALAST NP

Dosage Form: Injection, powder, lyophilized, for solution

Packaging: ARALAST NP will be supplied as a sterile, non-pyrogenic, lyophilized powder in single-dose vials. A suitable volume of Sterile Water for Injection, USP diluents will be provided (50mL/1.0 g vial and 25mL/0.5 g vial).

Labeling: The product will be labeled according to the valid regulatory requirements for clinical studies.

Storage: ARALAST NP should be stored at temperatures not to exceed 25˚C (77˚F). Do not freeze the product. Do not use after the expiration date printed on the label.

8.7.1.2 GLASSIA

Dosage Form: Injection, solution

Packaging: GLASSIA will be supplied as a sterile, non-pyrogenic, ready-to-use solution, in single dose vials containing 1 gram of functional A1PI in 50 mL of solution.

Labeling: The product will be labeled according to the valid regulatory requirements for clinical studies.

Storage: GLASSIA should be stored at 2-8˚C (36-46˚F). Do not freeze the product. Do not use after the expiration date printed on the label.

8.7.1.3 Placebo Solution

Human albumin 2% in normal saline will be used as the placebo control in this study. Human albumin 2% solution will be prepared at the pharmacy by appropriate dilution of human albumin at a concentration of 20 g/L or 25% with normal saline solution. Do not dilute human albumin solution with sterile water for injection.

Both human albumin product and normal saline solution should be inspected visually for particulate matter and discoloration. The products should not be used if particulate matter and/or discoloration are observed.

8.7.1.3.1 Human Albumin

Dosage Form: Injection, solution.

Packaging: Human albumin product 20 g/L or 25% will be supplied; the specific human albumin product available for the preparation of the placebo control may vary by region depending on the regional regulatory requirements.

Human albumin product 20 g/L or 25% is a transparent or slightly opalescent solution, which may have a greenish tint or may vary from a pale straw to an amber color.

Labeling: Human albumin solution will be labeled according to valid regulatory requirements for clinical studies.

Storage: Store human albumin product according to information provided in the specific product label. Do not freeze the product. Do not use after the expiration date printed on the label.

8.7.1.3.2 Normal Saline Solution

Dosage Form: Injection, solution.

Packaging: Normal saline solution is a ready-for-use, sterile, clear, colorless solution available in various volume sizes such as 250 mL, 500 mL, and 1000 mL.

Labeling: Normal saline solution will be labeled according to valid regulatory requirements for clinical studies.

Storage: Store normal saline solution at room temperature. Do not freeze the product. Do not use after the expiration date printed on the product.

8.7.2 Preparation of Infusion Solution

The dose (in mg) will be calculated based on the subject's body weight at screening, and at all subsequent office visits. The same dose (in mg/kg) is to be administered to an individual subject throughout the duration of the study. Adjustments based on body weight changes during the course of the study may be adjusted if necessary to maintain accurate dose (in mg/kg). Only body weight measurements obtained at study sites, using standardized techniques and a consistent well-maintained instrument may be used for dose calculations. Body weight collected during home infusion visits should try to be as consistent as possible, but will not be used to calculate dose – the weight from the previous office visit will be used.

The volume of infusion solution (in mL) will be calculated based on the content of functional A1PI (potency) in GLASSIA or ARALAST NP vials as printed on the product carton and vial. For instructions on the preparation and administration of GLASSIA or ARALAST NP infusion solution, please refer to the respective product package insert or IB.

To maintain blinding, all subjects will receive IP in two identical intravenous (IV) bags that are opaque or covered with opaque overwraps. Note: The person preparing the infusion solution will be unblinded. In the case of home infusion visits, the blinded IP will need to be prepared in advance by the unblinded pharmacist or other site professional and provided as blinded product to the home-infusion nurse.

8.7.3 Administration

Mode of administration: Intravenous infusion

- A 5-micron in-line filter will be used for all IP administrations.
- To maintain blinding, all subjects will receive IP in two identical IV bags that are opaque or covered with opaque overwraps. The person administering the infusion must be blinded to treatment.

Subjects in Group 1 and Group 3 will receive one IV bag of active IP and one volume-matched IV bag of placebo solution (human albumin 2% in normal saline).

Subjects in Group 2 and Group 4 will receive two identical IV bags of active IP.

Subjects in Group 5 will receive two identical IV bags of placebo solution (human albumin 2% in normal saline).

Rate of administration: 0.2 mL/kg BW/min
The rate of infusion will be regulated by an infusion pump delivering a constant rate of 0.2 mL/kg BW/minute.

If a moderate or severe AE occurs during infusion, the infusion rate may be reduced or the infusion be interrupted until the AE subsides, at the investigator's discretion. The infusion may then be resumed at a rate tolerated by the subject, but not to exceed 0.2 mL/kg BW/minute. Any reductions in infusion rate, interruptions or discontinuation of an infusion, as well as the reason for the reduction or interruption, will be recorded in the appropriate CRF(s). Any medications and/or non-drug therapies used to treat AE(s) must be recorded in the appropriate CRF(s).

8.7.4 Description of Treatment

8.7.4.1 Treatment Period

Treatment: Either ARALAST NP, GLASSIA, or Placebo

Treatment duration: 24 months (104 weeks)

Dose: 60 mg/kg BW/week, 120 mg/kg BW/week, or Placebo

Dosage frequency: Weekly

8.7.5 Investigational Product Accountability

The investigator/designee will ensure that the IPs are stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator/designee will maintain records that the IPs were received, including date received, drug identity code, date of manufacture and/or expiration date, amount received and disposition. IP must be dispensed only at the study site or other suitable location. Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially-used and/or unused IP will be returned to the sponsor or sponsor's representative or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP is to be destroyed, the investigator/designee will provide documentation in accordance with the sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study may include but not limited to the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, records entered into web and/or phone IRT system and/or any direct data capture system, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study. No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and case report forms (CRFs), see Section 17.2.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet ALL of the following criteria are eligible for this study:

1. Adults of either gender 18 years of age or older at the time of screening.
2. Endogenous plasma A1PI level < 8 μM at any time during the Screening period for treatment-naïve subjects, or following 4-weeks minimum wash-out from previous augmentation therapy in treatment-experienced subjects. The screening plasma A1PI level may be repeated if a subject obtains an exclusionary value that is suspected to be due to inadequate washout of A1PI).
3. Subject has documented A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, Pi*Null/Null, or other rare genotypes (except PI*MS, PI*MZ, or PI*SZ).
4. Clinically evident mild-moderate COPD (according to GOLD criteria for diagnosis) at the time of screening defined as follows:
   a. FEV_1 is ≥ 30% and ≤ 80% predicted
   b. If FEV_1 is > 80% predicted, then FEV_1/forced vital capacity (FVC) must be < 0.7 or DL_{CO} must be ≥ 30% and ≤ 65% predicted
5. If the subject is treated with any respiratory medications including inhaled bronchodilators, inhaled corticosteroids, or systemic corticosteroids (e.g. prednisone ≤ 10 mg/day or its equivalent), the doses of the subject's medications have remained stable for at least 28 days prior to screening.
6. No clinically significant abnormalities (other than emphysema, bronchitis or bronchiectasis) detected via a chest computed tomography (CT) or chest X-ray at the time of screening.
7. If female of childbearing potential, subject must have a negative pregnancy test at screening and agree to employ adequate birth control measures for the duration of the study.
8. Subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Known ongoing or history of clinically significant pulmonary impairment other than emphysema / COPD.
2. The subject is experiencing lower respiratory infection (LRTI)/acute pulmonary exacerbation (APE) at the time of enrollment (signing ICF). Subject may be re-screened after both clinical resolution of LRTI/APE and having also remained stable for at least 4 weeks after the end of LRTI/APE).
3. Known ongoing or history of cor pulmonale.
4. Known resting partial pressure of carbon dioxide ($PaCO_2$) levels of > 45 mmHg.
5. Clinically significant congestive heart failure with New York Heart Association (NYHA) Class III/IV symptoms.
6. The subject has received an organ transplant, has undergone major lung surgery, or is currently on a transplant list.
7. Known history of ongoing malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix).
8. Smoker or subject that has ceased smoking for less than one year prior to screening whose levels of cotinine are outside of the normal range of a non-smoker. All subjects must agree to refrain from smoking throughout the course of the study.
9. The subject is receiving long-term therapy (> 28 days) of parenteral corticosteroids or oral corticosteroids at doses greater than 10 mg/day of prednisone or its equivalent.
10. The subject is receiving long-term round-the-clock oxygen supplementation (other than temporary for acute COPD exacerbation, or supplemental O_2 with continuous positive airway pressure [CPAP], or bi-level positive airway pressure [BiPAP] during the day).
11. Subject has contraindications for CT (eg, body weight and/or body size exceeding the weight and gantry size limits specified by the manufacturer of the CT scanner, inability to lie flat in the CT scanner, claustrophobia, metal prosthesis or pacemaker in the chest wall or upper extremity that would impact lung density assessment).
12. Subject is unwilling or unable to modify bronchodilator medications for 6 hours for short acting β2 agonists, 24 hours for long-acting β2 agonists, and 48 hours for long acting anticholinergics prior to the scheduled quantitative CT scan.

13. Known severe immunoglobulin A (IgA) deficiency (ie, IgA level < 8 mg/dL at screening).
14. Known history of hypersensitivity following infusions of human blood or blood components (eg, human immunoglobulins or human albumin).
15. Presence of clinically significant laboratory abnormalities at the screening that meets one or more of the following criteria:
    a. Serum alanine aminotransferase (ALT) ≥ 3 times upper limit of normal (ULN)
    b. Serum total bilirubin ≥2 times ULN
    c. Proteinuria > +2 on dipstick analysis
    d. Absolute neutrophil count (ANC) ≤ 1500 cells/mm^3
    e. Hemoglobin (Hgb) ≤ 10.0 g/dL
    f. Platelet count ≤ 100,000/mm^3
    g. Serum creatinine ≥2 times ULN
16. The subject has a clinically significant medical, psychiatric, or cognitive illness, is a recreational drug/alcohol user, or has any other uncontrolled medical condition (eg, unstable angina, transient ischemic attack, uncontrolled hypertension) that, in the opinion of the investigator, would affect subject's safety or compliance or confound the results of the study.
17. Subject has been exposed to another IP within 28 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
18. Subject is a family member or employee of the investigator.
19. If female, subject is pregnant or nursing at the time of enrollment.

9.3 Withdrawal and Discontinuation

Any subject may voluntarily withdraw consent for continued participation and data collection. The reason for withdrawal will be recorded on the appropriate CRF. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) are described in Section 10.5 and Section 20.2.

Discontinuation may be due to subject dropout or being lost to follow-up, for example. Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects may be also withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through outcome of the pregnancy and up to 1 year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
2. The subject begins nursing. IP exposure will be discontinued. The investigator will record a narrative description of the course of the baby's development.
3. The subject receives any non-study A1PI product other than the IP provided.
4. The subject receives other investigational product(s) other than the IP provided in this study.
5. The subject is unwilling or unable to comply with the provisions of the protocol (eg, missing 4 consecutive product infusions of IP, unable or unwilling to undergo the scheduled assessments).
6. The subject starts/resumes smoking during study participation.
7. The subject withdraws consent.

The dosing and administration of investigational medication will be discontinued for an individual participant if *any* of the following criteria (which will also be considered serious adverse events) are met:

- Thromboembolic event, including deep vein thrombosis, pulmonary embolism, myocardial infarction
- Unstable angina
- Transient ischemic attack or stroke/cerebrovascular accident

The subject should be treated under the supervision of the investigator/designee in accordance with the local standard of care. The SAE must be reported to the sponsor within 24 hours as outlined in Section 2.

9.3.1 Study Discontinuation Due to Disease Progression

Subjects who continue to show rapid progression of COPD, as determined by a decline of PD15 lung density from baseline exceeding 1.5 x the upper bound of the 95% CI of that observed in the RAPID Study[26] will be discontinued from the study. In the RAPID Study, the upper bound of 95% CI of change in PD15 lung density was 1.42 g/L/year. Therefore, a decline in CT lung density exceeding 1.42 x 1.5 = 2.13 g/L/year will be used as criterion for discontinuation from the study. Data obtained prior to discontinuation will

be included in the primary efficacy analysis based on the full analysis set. Safety information will be collected throughout the participation of the patients in the study.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any subject who provides informed consent is considered enrolled into the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (eg, 460503) to be provided by the sponsor, 2- or 3-digit number study site number (eg, 02) to be provided by the sponsor, and 3- or 4- digit subject number (eg, 0003) reflecting the order of enrollment (ie, signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 460503-020003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The principal investigator (PI)/designee is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for any screening failures. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the study completion CRF should be completed, as applicable, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in the Figure 20-1. Details on the procedures to be performed at each study visit, including screening, can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

10.3.1 Screening

A subject's eligibility will be determined in accordance with the inclusion and exclusion criteria outlined in Section 9.1 and Section 9.2. The screening period may last up to 6 weeks. Screening procedures are outlined in Table 20-1.

Subjects who are currently receiving or have been recently treated with A1PI augmentation therapy within 4 weeks of screening will be required to have their pre-study A1PI augmentation therapy discontinued and undergo a washout period of at least 4 weeks in order for A1PI levels to return to their endogenous (pre-augmentation) level. Plasma A1PI levels will be assessed to verify adequacy of A1PI washout and to confirm diagnosis of A1PI deficiency. All other screening procedures may be performed prior to the completion of the washout period.

As part of the screening, the subject's medical history, medication and/or non-drug therapy, as well as smoking history will be recorded (see Section 12.5 and Section 12.6).

For eligibility determination, recent records of 12-lead ECG obtained within 26 weeks prior to screening may be used, if available. Blood pressure measurements must be obtained according to American Heart Association Guidelines published in 2005,[27] and may be repeated once, at least 1 week after the first collection in the event of exclusionary values obtained during the initial measurement, in order to verify eligibility.

The following screening laboratory tests may be repeated once, at least 1 week apart in the event of abnormal laboratory values or suspected erroneous values (see Section 9.2 Exclusion Criteria, exclusion criteria #12, #13, #16). If the follow-up assessments also fall outside of the protocol-specified accepted values, the subject will be counted as a screen failure.

Screening procedures will be postponed in the event of a moderate or severe LRTI/APE until clinical resolution of the LRTI/APE (ie, clinically evident signs or symptoms are no longer evident) and subject remains stable for at least 4 weeks after the end of the LRTI/APE.

10.3.2 Randomization

Randomization is to take place after a subject has completed all the screening procedures and met all eligibility criteria, but before the first IP administration during Week 1. See Section 8.5 for more details.

10.3.3 Treatment Period Visits

10.3.3.1 Week 1 Visit

During Week 1, baseline assessments for CT densitometry, pulmonary function tests (spirometry, DL_{CO}, and lung volumes), 6MWT, MMRC dyspnea scale, BODE index, SGRQ-C, and SF-36 will be conducted. These assessments may be performed on the same day as the IP infusion visit, but must be completed prior to start of the IP infusion.

10.3.3.2 Infusion Visits

During the study treatment period, the subject will receive weekly intravenous infusions of ARALAST NP or GLASSIA (60 mg/kg BW/week or 120 mg/kg BW/week), or placebo (human albumin 2% in normal saline) solution, for a period of 24 months, depending on the subject's treatment assignment. The IP infusion will be administered intravenously at a rate of 0.2 mL/kg/min as regulated via a variable rate infusion pump (see also Section 8.7.3). Scheduling of all infusion or study visits will be based on the date of the first IP infusion visit (Week 1, Day 1).

The first IP infusion will be administered under direct supervision at the study site to monitor for safety and tolerability. At the investigator's discretion, subsequent IP infusions may take place at the study site, or other suitable location, as acceptable per local regulations and standard practices of the study site. Exceptions are those IP infusions that are scheduled to occur during the same week as the clinic visits (at Weeks 4, 13, 26, 39, 52, 65, 78, 91, and 104; see Table 20-1, footnote k), which must be administered at study site to facilitate safety monitoring by the investigator. All IP infusions will be administered by a qualified healthcare professional.

During each infusion visit, vital signs (see Table 20-1) will be measured within 60 minutes prior to the start of an infusion and within 60 minutes after completion of the infusion. Vital signs will be measured when subjects are in the sitting position after a 5-minute rest.

Additionally, the following infusion-related information will be recorded for each IP infusion in the appropriate CRF(s):

- Date, start and end time of infusion
- Infusion volume (planned and actual)
- Infusion rate, as well as start and end time of each infusion rate
- Any changes in infusion rates, interruptions or discontinuation of an infusion, as well as the reason of infusion rate change/interruption/discontinuation
- Any AE(s) and use of any medications, and any non-drug therapies, to treat AE(s)

Following each infusion visit, telephone follow-up will be conducted by the investigator/designee at 72 hours (+ 1 business day) to document AEs, and/or administration of concomitant medications or non-drug therapies, which may have occurred within 72 hours after the completion of an infusion. Any adverse events that occur and/or concomitant medications/non-drug therapies that the subject takes after the

post-infusion telephone follow-up will be collected during the subsequent weekly infusion visit.

If a moderate or severe episode of APE occurs during the treatment phase, the subject should continue with the planned study visits and receive weekly IP infusions as scheduled, unless deemed medically inappropriate by the investigator.

10.3.3.3 Post-Baseline Study Visits

Following initiation of the treatment phase, subjects will be asked to return to the study site at Week 4 and then every 3 months (ie, every 13 weeks [± 2 days]) starting with Week 13 for safety monitoring (see Table 20-1). Physical examination, vital signs, and clinical laboratory assessments will be conducted during these visits (see Table 20-2 for a detailed list of laboratory tests to be conducted). Blood samples will be collected every 3 months for the monitoring of trough A1PI (antigenic and functional) levels in plasma and anti-A1PI antibodies in serum. Sample collection for the determination of plasma A1PI levels and for the presence of binding and/or neutralizing anti-A1PI antibodies must be collected within 4 hours prior to the start of the IP infusion on the day of an infusion visit.

Subjects will also be asked to return to the study site every 6 months (ie, every 26 weeks [± 2 days]) for clinical outcome and quality of life assessments (Weeks 26, 52, 78, and 104). In addition to the safety assessments mentioned above, other clinical assessments including CT densitometry, pulmonary function tests, 6MWT, MMRC dyspnea scale, and BODE index (that includes body weight measurements for the calculation of BMI),disease specific quality of life instrument (SGRQ-C), and general HRQoL (SF-36) will be administered. As tobacco use is a confounding factor in the assessment and analysis of clinical and health-related outcome measures in COPD, all subjects will be tested periodically (every 3 months) for cotinine level as a marker for tobacco use. Resumption/initiation of smoking during study participation will result in discontinuation of the subject from the study. In the event of a pulmonary exacerbation occurring during the study, planned study visits including those with a scheduled CT densitometry will be postponed for a minimum period of 4 weeks (or 90 days in the case of CT densitometry) following treatment of, and subsequent complete clinical resolution of any pulmonary exacerbation.

10.3.4 Study Completion Visit

The study completion visit will be conducted 1 week (±2 days) following the last IP infusion. See Table 20-1 for a list of assessments to be conducted at this study visit.

10.3.5 Early Termination Visit

Subjects who intend to withdraw or are being discontinued from study participation after being exposed to IP administration and subjects who are discontinued from study due to rapid progression (see Section 9.3.1) will be asked to undergo an early termination visit at 1 week (± 2 days) after the last infusion. See Table 20-1 for a list of assessments to be conducted at this study visit.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted during the course of the study:

- Any A1PI augmentation therapy other than IP provided for this study
- Other investigational product(s) other than the IP provided for this study

A subject who has taken these prohibited medications or received prohibited non-drug therapies will be considered a protocol deviation.

The following medications and non-drug therapies **are** permitted during the course of the study, provided that the dosages have remained stable for at least 28 days prior to screening:

- Inhaled bronchodilators
- Inhaled corticosteroids
- Low-dose systemic corticosteroids (prednisone ≤ 10 mg/day or its equivalent)

Note: Any medically necessary changes in the dose of corticosteroids must be approved by the sponsor or the sponsor's medical representative.

Medications to manage/treat acute pulmonary exacerbations are allowed at the investigator's discretion and may include:

- Inhaled beta-agonists
- Theophylline
- Systemic steroids
- Antibiotics

Note: In case of life-threatening exacerbations, any and all therapies and interventions deemed medically necessary by the treating physician may be prescribed.

For questions about medications and non-drug therapies that are not listed, please consult with the sponsor and/or the sponsor's representative.

All medications taken and non-drug therapies received will be recorded on the concomitant medications and non-drug therapies CRFs.

10.5 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she has completed all study procedures according to the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF. Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments and Supplement 20.3 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.6 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY

11.1 Lung Density by Computed Tomography

Computed Tomography (CT) scans will be used to measure lung density as a quantitative assessment of emphysema progression and treatment efficacy at each of the study visits described in Table 20-1.[28] Due to potential issues with scheduling, the CT may be completed within 1 week of the corresponding study infusion. See the CT lung densitometry acquisition and analysis manual for further details.

All CT scans will be analyzed by a central laboratory blinded to the patient randomization schedule.

The primary efficacy outcome will be measured by rate of change in CT lung density. CT lung density at the 15th percentile (PD15) is the threshold below which 15% of the voxels have lower densities, and is used as the parameter for estimating the rate of lung density decline. Along with PD15, other densitometry indices defined from the frequency distribution of histograms of lung voxels such as the mean lung density (MLD), Voxel index at a threshold of -910 Hounsfield Units (VI-910), and Voxel index at a threshold of -950 Hounsfield Units (VI-950) can be explored as supportive analyses of the rate of emphysema progression. The above mentioned analysis (ANCOVA) will be performed to test the treatment differences as mentioned above.

11.2 Pulmonary Function Tests

11.2.1 Spirometry

Spirometry assessments are to be conducted according to standard guidelines published by the American Thoracic Society and European Respiratory Society.[29;30] Whenever possible, all measurements should be performed with the same equipment at approximately the same time of day (± 2 hours) during site visits to minimize equipment and diurnal variability. All spirometric measurements (FEV_1 and FVC) are to be measured 30 ± 5 minutes following administration of a short-acting β-2 agonist bronchodilator (eg, a total of 400 µg of albuterol or salbutamol [2x 200 µg or 4 x 100 µg] or its equivalent). Spirometric measurements (FEV_1 and FVC) are to be performed in triplicate, and the highest value at each time point for each variable is to be used for analyses. The spirometry equipment is to be calibrated according to the manufacturer's recommendation and documented in a maintenance log. The same method for the calculation of predicted normal values will be applied for all subjects and assessment time points to maintain standardization.

Subject eligibility determination will be based on spirometric measurements taken at screening. Subsequent spirometry tests will be performed at the study visits described in Table 20-1 (see Pulmonary Function Tests). At visits when infusions are administered, spirometry assessments must occur prior to the IP infusion. In addition, the assessments are to be performed according to the same procedure used at screening throughout the study.

11.2.2 Single-Breath Determination of Carbon Monoxide Uptake in the Lung (DL_{CO})

DL_{CO} will be measured using the single-breath technique, which involves the measurement of carbon monoxide uptake from the lung over a single breath-holding period (10 ± 2 seconds). The test gases used should contain a mixture of carbon monoxide (nominally ~0.3%), a tracer gas (eg, 10% helium), oxygen and nitrogen. In order to minimize test variability, all determinations will be conducted in accordance with recommendations for the standardization of testing published by ATS and ERS[31;32] and general guidelines for lung function testing.[30] Whenever possible, all measurements should be performed with the same equipment around the same time of day during site visits, to minimize equipment and diurnal variability. In addition the tests are to be performed according to the same procedure used at screening throughout the study. Gas volumes are reported with body temperature and pressure saturated corrections and results are expressed in absolute values and as percentage of predicted values.

Single breath determination of DL_{CO} will be performed at the study visits described in Table 20-1 (see Pulmonary Function Tests). At visits when infusions are administered DL_{CO} assessments must occur prior to IP administration.

11.2.3 Measurement of Lung Volumes

Lung volume assessments are dependent on the accurate measurement of the volume of gas in the lungs at a resting end-expiration, known as the Functional Residual Capacity (FRC). The maximum amount of gas that can be inspired from FRC is referred to as the inspiratory capacity (IC). Total lung capacity (TLC) refers to the volume of gas in the lungs after maximal inspiration, or the sum of all volume compartments. TLC typically is determined by using 1 of 2 techniques, helium dilution/equilibration and whole-body plethysmography. Plethysmography uses Boyle's law to measure the compressible gas volume within the thorax and is more accurate than gas dilution techniques. Whole body plethysmography is the recommended method to be used in this study, however, other methods, such as or helium dilution may be utilized if plethysmography is not available.

Determination of lung volumes including TLC, FRC, RV, and IC will be performed at the study visits described in Table 20-1 (see Pulmonary Function Tests).
At visits when infusions are to be administered, IC and TLC assessments must occur prior to the IP administration. In addition, in order to minimize test variability, all determinations will be conducted using the same procedures that are used to collect screening and baseline measurement (prior to the first IP administration during Week 1) and in accordance with recommendations for the standardization of testing published by ATS and ERS[32] and general guidelines for lung function testing.[30] Whenever possible all measurements for a given subject should be performed with the same equipment around the same time of day during site visits to minimize equipment and diurnal variability.

11.3 Pulmonary Exacerbation

Throughout the study, the frequency, duration and severity of COPD exacerbations will be evaluated using the criteria established in the UPLIFT clinical study.[33] An exacerbation is defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and / or systemic steroids.[33] The severity of an exacerbation will be categorized according to the following definitions:

- Mild – treated at home without seeing a health care provider
- Moderate – visit with health care provider (eg, home visit, visit to an outpatient facility or an emergency department -but not requiring overnight admission to hospital)
- Severe – hospitalization (including an emergency department stay >24 hours)

Detailed information on COPD exacerbations including hospitalizations due to exacerbations and respiratory medications administered for the treatment of an exacerbation will be collected.

11.4 Six Minute Walk Test (6MWT)

6MWT will be performed according to current ATS guidelines (2002)[34] at the study visits described in Table 20-1. The 6MWT should be performed about the same time of a day for each assessment visit to minimize intraday variability. At visits when infusions are administered, the 6MWT must be performed prior to the IP administration.

11.5 Modified Medical Research Council (MMRC) Dyspnea Scale

Functional dyspnea will be assessed through the modified MMRC dyspnea scale.[35-37] The MMRC dyspnea scale is a useful method for grading the effect of breathlessness on mobility.[35] The scale has 5 grade points from 0 through 4 that describe the extent of perceived breathlessness and its impact on daily activities (see Table 11-1).

Table 11-1
MMRC Dyspnea Scale

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Trouble by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Functional dyspnea assessment should be administered on the same day of BODE index assessment at the study visits described in Table 20-1. At visits when infusions are administered, functional dyspnea assessment must occur prior to the IP administration.

11.6 BODE Index

The BODE index is a multidimensional grading system incorporating body mass (B), degree of airflow obstruction (O), functional dyspnea (D), and exercise capacity (E). BODE index is computed based on FEV_1 (% predicted), distance walked in 6 minutes, MMRC dyspnea scale, and BMI with each variable being graded between 0 to 3 and summed to give a total score between 0 to 10 (see Table 11-2). The higher the BODE index scores indicates a greater risk of death. The BODE index has been demonstrated to be better than FEV_1 alone at predicting the risk of death from any cause and from respiratory causes among subjects with COPD.[37]

BMI is calculated by dividing body weight (in kg) obtained during each study site visit (see Table 20-1) by the square of the height (in meters) obtained at screening. The degree of airflow obstruction is assessed by post-bronchodilator FEV_1 (% predicted). Functional dyspnea is evaluated based on the modified MMRC dyspnea scale, as described below in

Table 11-2. Exercise capacity is measured by the distance walked (in meters) in 6 minutes in the 6MWT, as described in Section 11.4.

Table 11-2
Variables and Point Values Used For the Computation of the BODE Index

Variable	Points on BODE Index			
	0	**1**	**2**	**3**
FEV_1 (% of predicted)	≥ 65	50 – 64	36 - 49	≤ 35
Distance walked in 6 minutes (m)	≥ 350	250 – 349	150 - 249	≤ 149
MMRC dyspnea scale	0 – 1	2	3	4
BMI (kg/m^2)	> 21	≤ 21	-	-

BODE index evaluation will be performed at the study visits described in Table 20-1. At visits when infusions are administered, the BODE index evaluation must occur prior to the IP administration.

11.7 St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C)

The SGRQ-C is a disease-specific instrument designed to measure health impairment and quality of life among patients with chronic airflow limitations, and has been validated for COPD.[38] The instrument consists of 40 items in two parts: Part 1 (Questions 1-7) which addresses the frequency of respiratory symptoms, and Part 2 (Questions 8-14) which addresses the patient's current state with respect to the subject's activity activities that cause or are limited by breathlessness and the impact of the disease on the subject's psycho-social function. Three component scores (Symptoms, Activity, Impacts) and a Total score will be calculated. Scores range from 0 to 100, with higher scores indicating more limitations. As missing items may have an impact on individual section scores and total score, subjects should be encouraged to complete the questionnaire without missing items. Detailed scoring algorithm and handling of missing items are described in the SGRQ-C manual.

The SGRQ-C will be administered using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. See Table 20-1 for the timing of assessments.

11.8 Short Form-36 Health Survey (SF-36 v. 2)

The Short Form (SF)-36 (version 2) health survey[39] will be utilized to assess changes in health-related quality of life and functional health. The SF-36 health survey is a standardized, validated instrument designed to be self-administered by subjects aged 14 years and older, and is composed of items grouped into 8 domains. The domains reflected in the physical component summary score (PCS) are physical functioning, role-physical, bodily pain, and general health. The domains captured in the mental component score (MCS) include social functioning, role-emotional, vitality, and mental health.

The SF-36 health survey will be administered at the study site using a validated translated version, as applicable. It is recommended that the subject complete the assessment using the same translated version throughout the course of the study. See Table 20-1 for the timing of assessments.

11.9 Plasma Antigenic and Functional A1PI Levels

Throughout the treatment period, plasma trough A1PI levels will be assessed to monitor the increase in, and maintenance of circulating A1PI levels at target of 11 µM or greater. Plasma samples for the determination of trough antigenic A1PI and functional A1PI (also known as ANEC) levels will be collected prior to the first IP infusion during Week 1, on the day of IP administration (must be collected within 4 hours prior to the start of IP infusion) during Weeks 13, 26, 39, 52, 65, 78, 91, and 104 (last IP infusion visit) during treatment period, as well as during the study completion (Week 105) visit (see Table 20-1 and Table 20-2).

Subjects who are discontinued early from the study after having been exposed to IP will be asked to have a plasma sample collected for A1PI determination. The early termination plasma sample will be analyzed to support analysis/interpretation of the early termination anti-A1PI antibody assessment.

Sample analyses for the determination of plasma antigenic and functional A1PI levels will be performed using bioanalytical assays at a qualified laboratory.

11.10 Exploratory Biomarkers

[redacted]

[redacted]

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

A **serious** adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), HBV, HCV, hepatitis E virus (HEV), or parvovirus B19 (B19V)

- Thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accidents [e.g., stroke, transient ischemic event])

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

12.1.1.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.3 Adverse Reactions (ARs) Plus Suspected Adverse Reactions

An AR plus suspected adverse reaction is any adverse event which met any of the following criteria:

(a) an adverse event that began during infusion or within **72** hours following the end of IP infusion, or

(b) an adverse event considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or

(c) an adverse event for which causality assessment was missing or indeterminate.

In addition, safety data will also be analyzed for any ARs plus suspected adverse reactions which met any of the following criteria:

(a) an adverse event that began during infusion or within **24** hours following the end of IP infusion, or

(b) an adverse event considered by either the investigator and/or the sponsor to be possibly or probably related to IP administration, or

(c) an adverse event for which causality assessment was missing or indeterminate.

12.1.1.4 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (eg, IB, package insert). “Unexpected” also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. The expectedness of AEs will be determined by the sponsor using the IB and/or prescribing information as the RSI. This determination

will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

12.1.1.5 Preexisting Diseases

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

Any pulmonary exacerbations (see Section 11.3) will be captured as adverse events, as well as any respiratory symptoms that worsen in intensity or frequency during the course of the study.

12.1.1.6 Adverse Reaction

An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began during or within 72 hours following the end of an IP administration, (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to IP administration, or (c) an adverse event for which causality assessment was missing or indeterminate.

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study completion/discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution, medically

stabilized, or 30 days after the study completion/early termination visit, whichever comes first. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported. Deviations from the protocol-specified dosage (including overdosing [by >50%], underdosing [by >50%], abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Notification Form within 24 hrs. of awareness and followed-up at 1 year post-delivery, if feasible. (S)AEs associated with these events must be reported on the appropriate (S)AE forms. If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the SAE Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequela/sequelae.

- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiologic plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP

- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
  - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 72 hours of the last IP administration, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences Not Considered Adverse Events

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the SAE Report. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the first IP exposure will be recorded on the AE CRF; however, these events will not be considered as AEs or included in the analysis of AEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary. In addition, the subject's medical history specifically related to COPD (such as time of first symptoms and time since diagnosis, as available), as well as A1PI

deficiency (such as previously documented α1-PI genotype or phenotype, as well as endogenous α1-PI level prior to receiving A1PI augmentation therapy) will be collected.

The subject's medication history (eg, use of A1PI augmentation therapy, bronchodilator, and steroid) and/or non-drug therapies (eg, oxygen supplementation) specifically related to the management of AATD and emphysema / COPD within 60 days prior to screening throughout the study, will be recorded on the appropriate CRF(s). All other medications taken and non-drug therapies received from 4 weeks before enrollment until study completion/discontinuation date will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Smoking History

Subject's smoking history including number of years of active smoking, number of packs smoked per day, and date of smoking cessation will also be recorded on the appropriate CRF.

12.7 Physical Examinations

At screening and subsequent study visits (as described in Table 20-1), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 12.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.8 Vital Signs

Height (in or cm) will be measured at screening only.

Body weight (lb or kg) will be measured and BMI (kg/m^2) will be determined at screening and each study visit as outlined in Table 20-1.

Other vital signs include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Blood pressure measurements must be obtained according to American Heart Association Guidelines

published in 2005[27] (see also Section 10.3.1). Vital signs will be recorded at the study visits as described in Table 20-2.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 12.1) and record the medical diagnosis (preferably), symptom, or sign on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Electrocardiogram

A 12-lead standard ECG will be performed at screening and following the last IP infusion at Week 104. For eligibility determination, recent records of 12-lead ECG obtained within 26 weeks prior to screening may be used, if available.

12.10 Immunogenicity

Serum samples for monitoring the appearance/presence of anti-A1PI antibodies will be collected prior to the first IP infusion during Week 1, on the day of IP administration (must be collected prior to the start of IP infusion) during Weeks 13, 26, 39, 52, 65, 78, 91, and 104 (last IP infusion visit) during treatment period, as well as during the study completion (Week 105) visit (see Table 20-1 and Table 20-2).

Subjects who are discontinued early from the study after having been exposed to IP administration will be asked to have a serum sample collected for anti-A1PI antibody determination.

Unscheduled samples for the detection of circulating anti-A1PI antibodies may be collected as necessary and upon consultation with or notification by the sponsor, to support investigation of suspected immune-related adverse events. At any scheduled or unscheduled time points, plasma samples for the determination of circulating A1PI levels will be collected concurrently to assess potential interference with the assay and to interpret antibody results.

Serum samples will be analyzed for the presence of antibodies against A1PI using a validated anti-A1PI antibody detection (screening and confirmatory) assay at a qualified immunoassay laboratory. Samples with confirmed positive titers will be further analyzed for the presence of neutralizing antibodies using a validated neutralizing antibody assay at a qualified immunoassay laboratory. Each sample for immunogenicity assessment is to

be stored as duplicate aliquots each with sufficient volume needed for sample analysis; one of the two aliquots will serve as the retention (backup) sample. Detailed sample handling and storage instructions will be provided in the laboratory manual.

12.11 Clinical Laboratory Parameters

12.11.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count [hemoglobin (Hgb), hematocrit (Hct), erythrocytes (ie, red blood cell (RBC) count), leukocytes (ie, white blood cell (WBC) count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet count.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, phosphorus, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl-transferase (GGT), creatine phosphokinase (CPK), bilirubin (direct and total), blood urea nitrogen (BUN), uric acid, creatinine, and glucose.

Samples in the appropriate matrix (as specified in the laboratory manual) for the assessment of hematology and clinical chemistry parameters will be performed at the study visits described in Table 20-2. At any time during the study, unscheduled hematology and/or clinical chemistry test(s) may be performed as part of AE/safety investigation or may be repeated once in the event of abnormalities in test results due to errors.

Hematology and clinical chemistry assessments will be performed at the central laboratory following standardized assay procedures.

12.11.2 Serum IgA

Serum IgA levels will be measured at screening only (see Table 20-2) for the determination of eligibility. Serum IgA measurements will be performed using an assay with a lower limit of quantification (LLOQ) of 8 mg/dL or lower.

12.11.3 Viral Serology

Serum samples will be collected for viral serology tests at screening and at study completion/early termination visits (see Table 20-2). Assessments will include HAV antibody, HBsAg, HCV antibody, and HIV-1/HIV-2 antibody tests, as well as B19V serology and nucleic acid test (NAT), which will be performed at the central laboratory.

Any seroconversion results shall be re-tested and additional tests for investigation may be conducted, in particular in the event of absence of clear alternative etiology.

12.11.4 Urine Tests

Urinalysis will consist of color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate, leukocyte esterase, and microscopic examination (RBC, WBC, bacteria, casts). Urine sample for urinalysis assessment will be collected at screening and analyzed at a central laboratory.

Pregnancy test will be performed for females of childbearing potential at screening and at study completion visit (see Table 20-2). Subjects who are discontinued early from the study will be asked to undergo urinalysis and urine/serum pregnancy test (for females of childbearing potential only) at the Early Termination visit, only if these subjects have been exposed to IP. Urine pregnancy test will be performed, unless serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.

12.11.5 Assessment of Laboratory Values

The investigator's assessment of each abnormal laboratory value will be recorded on the appropriate CRF/laboratory form. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes an new AE (see definition in Section 12.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 12.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, ie, because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

12.11.6 Back-Up Samples

Backup samples should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing (eg, in the event of erroneous or outlier assay results), further laboratory testing to support investigation of an AE, or as follow-up testing based on initial laboratory results. The following samples are planned:

- Plasma samples collected for the determination of the following analytes will each be split into duplicate aliquots of approximately equal volume (one of the 2 aliquots will serve as the backup sample):
    - Plasma antigenic A1PI
    - Plasma functional A1PI (ie, ANEC)
- Serum samples collected for the determination of the following analytes will each be split into duplicate aliquots of approximately equal volume (one of the 2 aliquots will serve as backup sample):
    - Anti-A1PI antibodies for screening and confirmatory binding antibody assays
    - Anti-A1PI antibodies for neutralizing antibody assay

Samples will be stored in a coded form for up to 2 years after the final study report has been completed, unless otherwise notified by the sponsor. The samples will be destroyed or transferred to another location upon notification by the sponsor.

13. STATISTICS

13.1 Sample Size and Power Calculations

The sample size proposed for this study will permit estimates of averages and variances in the rate of change of lung density and other parameters after 24 months of treatment in each treatment group and pooled within product. Information from this study will be used in the planning for a larger Stage 2 study. This study will not be powered to permit hypothesis tests of primary or secondary outcome measures.

13.2 Datasets and Analysis Cohorts

For definitions on datasets, refer to Section 13.4.1.

13.3 Handling of Missing, Unused, and Spurious Data

Statistical techniques will not be used to identify and exclude any observations as outliers from the analyses. If any data is considered spurious, eg, for lack of biological plausibility, it will be documented to include the reason for exclusion and the analyses from which the data points were excluded.

13.4 Methods of Analysis

All data analysis will be performed using SAS v. 9.1.3 or higher. Analytical methods for primary, secondary and exploratory outcome measures are each described in sub-sections below. Additional exploratory analyses of correlations between mean trough A1PI levels and various parameters and between CT lung density rate of change and various parameters are presented in Section 13.4.6.

13.4.1 Analysis Sets

The full analysis set (FAS), the modified full analysis set (mFAS), the per-protocol analysis set (PP), and safety analysis set (SAS) will be used for analyses.

- Full analysis set (FAS)
  The FAS will include all randomized subjects who have at least one CT scan.
- Modified full analysis set (mFAS)
  The mFAS will include all randomized subjects who have a baseline CT scan and at least one scan during the 24 months of treatment.
- Per Protocol Analysis Set (PP)
  The PP will be a subset of the mFAS analysis set and will exclude subjects meeting the following criteria:
    a. missing more than 4 consecutive doses
    b. subjects receiving < 80% planned infusions
- Safety Analysis Set (SAS)
  The SAS will include all subjects receiving study drug at least once, regardless of protocol deviations or non-adherence to study procedures.

13.4.2 Primary Outcome Measure

The primary efficacy outcome will be measured by rate of change in CT densitometry. CT lung density at the 15th percentile (PD15) is the threshold below which 15% of the voxels have lower densities, and is used as the parameter for estimating the rate of lung density decline.

13.4.2.1 Slope Analysis

Analyses will be conducted on the rate of change of lung density as measured by CT scan of the lung and based on Group 1 and Group 2 (ARALAST NP) versus placebo and Group 3 and Group 4 (GLASSIA) versus placebo. The primary analysis will be based on the FAS, and those based on the mFAS and PP will be considered supportive analyses. No explicit imputation of missing values will be performed for these analyses as SAS procedure PROC MIXED treats incomplete subject profiles in the sense that missing values are implicitly handled under the missing at random assumption.

A random coefficient model will be fitted, accounting for the fixed effect of treatment group, and the logarithm of baseline lung volume as a covariate. For slopes and intercepts an unstructured covariance structure will be assumed.

This model is described by the following equation:

$$y_{ijk}=\mu_k+\beta_{0jk}+(\beta_{1k}+\beta_{1jk}).t_i+\beta_2.\log(TLV_{jk})+\varepsilon_{ijk}$$

where

μ_k is the fixed effect of group *k (k=1,…,5)*

β_{0jk} is the random intercept for subject *j* in group *k*

t_i is timepoint *i* in years, t_i in {0, 0.5, 1, 1.5, 2}– considered to be a continuous variable

y_{ijk} is the lung densitometry value of subject *j* in group *k* measured at timepoint *i*

β_{1k} is the mean slope (yearly decline rate) for treatment group k

β_{1jk} is the random departure from the mean slope β_{1k} for subject *j* in group *k*

β_2 is the slope corresponding to the lung volume effect

TLV_{jk} is the total lung volume of subject *j* in group *k* at baseline

ε_{ijk} is the residual error for subject *j* in group *k* at timepoint *i*

$\varepsilon_{ijk} \sim N(0,\sigma^2)$ i.i.d.

$\beta_{1jk} \sim N(0, \sigma_1^2)$ i.i.d.

Mean rates of changes and 95% confidence intervals (CIs) will be estimated within this model by pooling data from both dose levels for each product separately, and they will be compared to the mean rates of changes in placebo (for the primary outcome measure).

Through the "random" statement in SAS proc mixed module we will provide the individual slopes and intercepts which will enable the estimation of group means and 95% CIs.

13.4.2.2 Change from Baseline Analysis

Treatment differences between Group 1 and Group 2 (ARALAST NP) versus placebo and Group 3 and Group 4 (GLASSIA) versus placebo using the mITT (as primary) for primary efficacy outcome measure will also be tested using an analysis of covariance (ANCOVA) approach, with the change from baseline to the last CT lung density scan as the dependent variable, and the baseline CT and the logarithm TLV as covariates. The mean changes in CT values from baseline to the end of treatment and respective 95% CIs will be estimated. Exploratory analyses may also be conducted with the addition of pulmonary function parameters, use of systemic glucocorticoids, smoking history, and gender as covariates in the models.

13.4.2.3 Sensitivity Analyses

A decline in lung density over time is expected due to the nature of the disease, whereby the decline is expected to be smaller in the treatment groups than in the placebo group. If CT assessments are missing, a worst case imputation method will be considered for handling dropouts for the FAS.

A worst case analysis is defined by imputing the missing CT assessments due to dropouts with the best possible outcome to the placebo group and the worst possible outcome to the treatment groups according to the following conservative method:

1. If an CT baseline assessment is missing for a subject, the missing values will be imputed for control and treatment groups as follows:
    a. Control group:
        i. The first valid CT value after the missing baseline value will be used to impute the missing baseline value.

b. Treatment groups:
    i. The maximum relative decrease from baseline will be calculated among all subjects with valid assessments at baseline and at the time point with the first valid CT assessment for the subject with the missing value as ratio of post-baseline / baseline values.
    ii. The missing baseline value is then imputed by multiplying the valid CT post-baseline value with the reciprocal of this ratio.

2. If intermediate CT assessments are missing for a subject at specific time points for treatment or control groups, the missing values will be imputed by linear interpolation whereby the last valid value before the missing value and the first valid value after the missing value are used for the interpolation.
3. If an CT assessment is missing for a subject at a specific time point and all subsequent time points (ie, monotone missing pattern due to a potential dropout of this subject), the missing values will be imputed for the control and treatment groups as follows:
    a. Control group:
        i. The last valid CT value before the first missing value will be used to impute the missing values for all subsequent time points.
    b. Treatment group:
        i. The maximum relative decrease from baseline is calculated among all subjects with valid assessments at baseline and at the time point with the missing post-baseline CT assessment for the subject with the missing value as ratio of post-baseline / baseline values.
        ii. The missing post-baseline value is then imputed by multiplying the baseline value with this ratio.

If the results of this extreme analysis based on the FAS are still favorable, it can be confidently concluded that they are robust to the handling of missing data.

13.4.3 Secondary Outcome Measures

13.4.3.1 Efficacy

The secondary outcome measure for efficacy is rate of change of lung density for each product at each dose level. The same model as for the primary outcome measure will be utilized to obtain estimates of mean rates of change of lung density per product per dose level using the FAS (as primary) and the mFAS and PP as supportive analyses.

Mean rates of changes and 95% CIs will be estimated within this model for each product at each dose level separately, and they will be compared to the mean rates of changes in placebo.

Graphs showing CT lung densities over time will be prepared, data permitting.

13.4.3.2 Pharmacokinetics

Mean steady state trough concentration levels of antigenic and functional A1PI will be summarized per dose per product and will be based on the safety analysis set.

13.4.3.3 Safety

For all secondary safety endpoints, point estimates (95% CI) for the respective parameter will be estimated. All summaries of AEs, temporally related AEs, and suspected adverse reactions plus ARs will be conducted by MedDRA term and by organ system for each treatment group separately, for each product (pooling data from Groups 1 and 2 for ARALAST NP, and from Groups 3 and 4 for GLASSIA) and by dose level (pooling data from Groups 1 and 3 for 60 mg/kg BW/week, and from Groups 2 and 4 for 120 mg/kg BW/week) respectively.

The following safety parameters will be summarized:

1. Number and rate of related and unrelated serious and non-serious AEs
2. Number and rate of temporally related serious and non-serious AEs (ie, AEs which began during or within 72 hours following the end of IP infusion)
3. Number and rate of suspected adverse reactions plus adverse reactions (ARs)
4. Number (proportion) of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped due to AEs
5. Number (proportion) of subjects who develop anti-A1PI antibodies following treatment with ARALAST NP or GLASSIA

AEs occurring during or after infusions will be summarized by seriousness, severity, and relatedness to study treatment.

Changes in chemistry and hematology parameters will be summarized using descriptive statistics and will be presented graphically and shift tables will be prepared accordingly.

These analyses described in this section will be based on the safety analysis set.

13.4.4 Exploratory Outcome Measures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.4.5 Subgroup Analyses

Subgroup analyses of rates of changes of lung density (as estimated by the model), pulmonary exacerbations, and changes in pulmonary functions parameters will be performed by BODE index score, sex, race, age, tertile of baseline lung density, and baseline FEV_1.

Categories for the BODE index scores such as 0-3, 4-6, and 7-10 will be employed. Age and baseline FEV_1 will be categorized by their observed quartiles.

13.4.6 Additional Exploratory Correlation Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.5 Planned Interim Analysis of the Study

Not applicable, no interim analyses are planned for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Trial Agreement.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.3.1 Safety Monitoring

The safety of the subjects in this study shall be monitored by an external data monitoring committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of pulmonary clinical care and research who are not actively recruiting subjects. The DMC will recommend to the sponsor whether to continue or stop the trial or to continue the study after proper amendment to the protocol.

15.4 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the audit plan.

15.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements and ICH GCP. An assent form may be provided and should be signed by patients less than 18 years of age. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which has been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study (see Section 16.3).

16.4 Data Monitoring Committee

This study will be monitored by Data Monitoring Committee (DMC). The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of alpha$_1$-proteinase inhibitor deficiency and COPD clinical care and research who are not actively recruiting subjects.

The DMC will be responsible for monitoring the safety of the study participants including periodic review of SAEs, AEs, and any relevant information that may have an impact on the safety of the participants or the ethics of the trial. Based on data review, the DMC may make a recommendation to continue the study as is, temporarily suspend the study, or terminate the study based on pre-defined criteria such as unacceptable toxicities or lack of treatment benefits. The membership, responsibilities, interactions, and operations of the DMC in providing oversight of the study, as well as criteria for DMC recommendations, are detailed in the DMC Charter.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, enrollment and screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry

will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided electronically.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data are not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

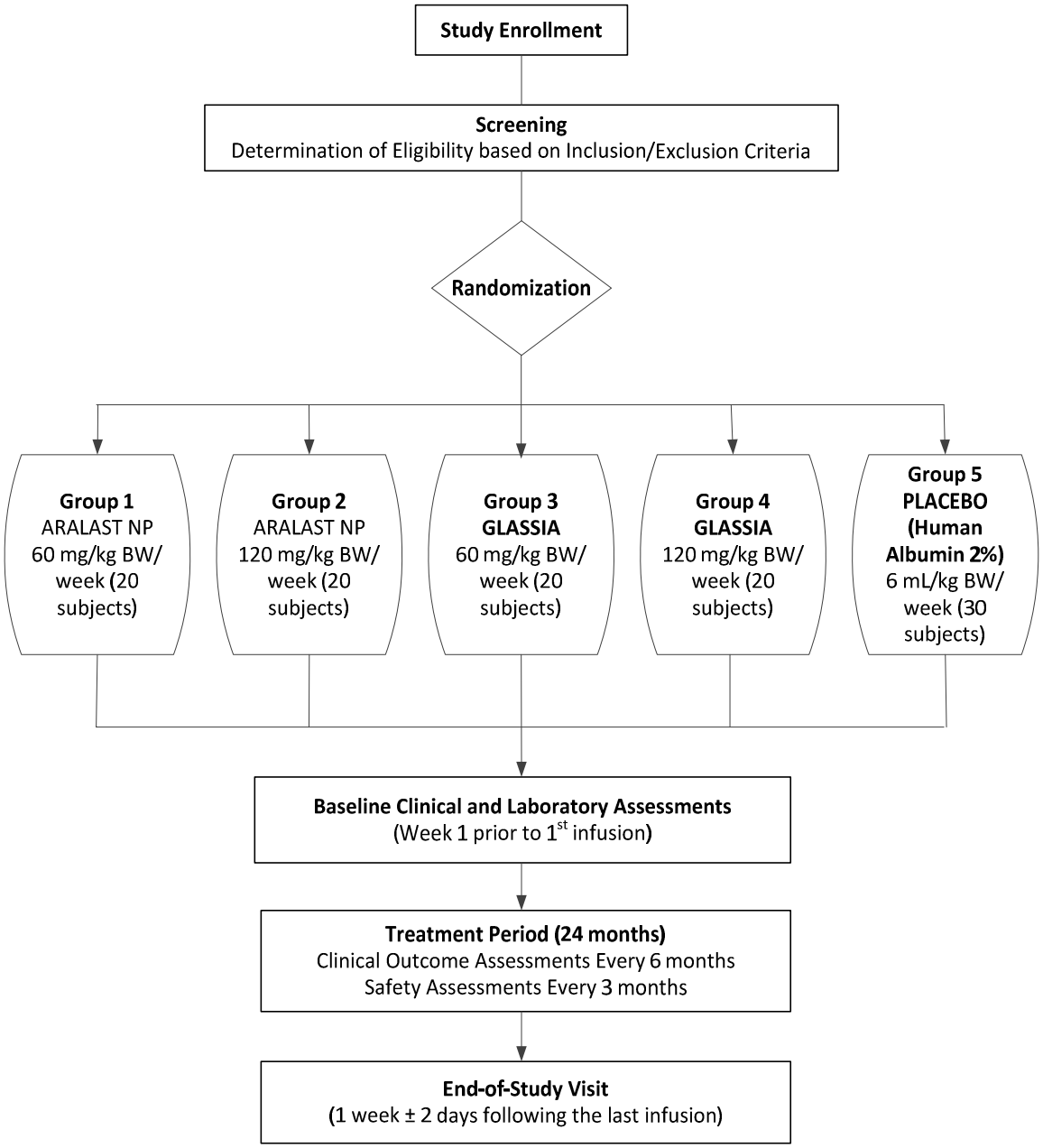
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 20-1
Study Flow Chart



20.2 Schedule of Study Procedures and Assessments

Table 20-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment		Treatment Period										Study Completion	Early Termination
	Scr (Max 6 Weeks)	Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Informed Consent[a]	X												
Eligibility Determination	X												
Demographics	X												
Medical, Medication, and Non-Drug Therapy History	X												
Smoking history	X												
Body Height	X												
Body Weight[b]	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
BMI	X	X			X		X		X		X		X[c]
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X[e]										X		
Chest X-Ray/CT	X												
Pulmonary function tests[f]	X	X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]

Table 20-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment		Treatment Period										Study Completion	Early Termination
	Scr (Max 6 Weeks)	Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Lung density CT scan[i]		X[g,h]			X[g,i]		X[g,i]		X[g,i]		X[g,i]		X[c]
6MWT		X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
MMRC dyspnea scale		X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
BODE Index		X[g,h]			X[g]		X[g]		X[g]		X[g]		X[c]
HRQoL (SGRQ-C and SF-36)		X[g,h]			X		X		X		X		X[c]
Clinical Laboratory Assessments[j]	X	X[g,h]	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
COPD Exacerbations	X	Weekly (Weeks 1 – 104)										X	X
IP Treatment[k]		Weekly (Weeks 1 – 104)											
Telephone follow-up[l]		Weekly (Weeks 1 – 104)											

Table 20-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment		Treatment Period										Study Completion	Early Termination
	Scr (Max 6 Weeks)	Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Concomitant Medications and non-drug therapies	X	Weekly (Weeks 1 – 104)										X	X
Adverse Events	X	Weekly (Weeks 1 – 104)										X	X

Abbreviations: Scr = Screening; BMI = Body mass index; ECG = Electrocardiogram; CT = Computed tomography; 6MWT = 6-minute walk test; MMRC = Modified Medical Research Council; BODE = Body mass index, airflow obstruction, dyspnea, and exercise capacity index; HRQoL = Health-related quality of life; SGRQ-C = St. George respiratory questionnaire for chronic obstructive pulmonary disease (COPD) patients; IP = Investigational product.

[a.] Written informed consent must be obtained prior to any study procedures including screening.

[b.] The subject's body weight measured at each office visit will be used to calculate the infusion volume (mL) for IP administration. Adjustment based on body weight changes during the course of the study may be made if necessary.

[c.] To be performed only if the last assessment is performed more than 13 weeks prior to the early termination visit.

[d.] Vital signs including body temperature, heart rate, blood pressure, and respiratory rate will be measured at screening, during each infusion visit (within 60 minutes prior to the start of an IP infusion and within 60 minutes after the end of an IP infusion), and at the study completion/early termination visit. Vital signs will be measured when subjects are in the sitting position after a 5-minute rest.

[e.] 12-Lead ECG previously obtained within 26 weeks prior to screening may be used, if available.

[f.] Pulmonary function tests include spirometry (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]), single-breath diffusing capacity of carbon monoxide (DL_{CO}), and lung volume measurements (total lung capacity [TLC], functional residual capacity [FRC], residual volume [RV], and inspiratory capacity [IC]). Spirometry is to be performed before and at 30 (± 5) minutes following inhalations of a short-acting inhaled bronchodilator (eg, salbutamol bromide at a total dose of 400 µg [2 x 200 µg or 4 x 100µg puffs] or its equivalent). Measurements of diffusing capacity and lung volumes are to be performed prior to bronchodilator administration and spirometry.

[g.] To be performed prior to IP administration.

Continued on Next Page

Continued

[h.] Values obtained prior to initiation of IP treatment during Week 1 visit will serve as the baseline values.

[i.] Subjects must have met all eligibility criteria prior to undergoing the baseline CT scans of the lungs (Week 1 prior to IP infusion). Subsequently, subjects will undergo CT assessment every 26 weeks (± 1 week) or early termination visit. See the CT lung densitometry acquisition and analysis manual for further details.

[j.] For laboratory assessments, see Table 20-2.

[k.] The first IP infusion must take place at the study site. At the investigator's discretion, subsequent infusions may be administered at the study site or at another suitable location by a qualified healthcare professional, except for those that occur in the same week as the clinic visits during Weeks 4, 13, 26, 39, 52, 65, 78, 91, and 104 described in the table above.

[l.] Following each infusion visit, telephone follow-up will be conducted by the investigator/designee at 72 hours (+ 1 business day) to document AEs, and/or administration of concomitant medications or non-drug therapies, which may have occurred within 72 hours after the completion of an infusion. Any adverse events that occur and/or concomitant medications/non-drug therapies that the subject takes after the post-infusion telephone follow-up will be collected during the subsequent weekly infusion visit.

20.3 Clinical Laboratory Assessment

Table 20-2
Clinical Laboratory Assessments

Procedure/ Assessment	Scr (Max 6 Weeks)	Treatment Period										Study Completion	Early Termination
		Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Hematology[a]	X	X[b,c]	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[d]	X	X[b,c]	X	X	X	X	X	X	X	X	X	X	X
Serum IgA	X												
Viral Serology[e]	X											X	X
Cotinine	X	X		X	X	X	X	X	X	X	X		X
Plasma A1PI (antigenic)	X	X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Plasma A1PI (functional)		X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Anti-A1PI Binding Antibodies		X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Anti-A1PI Neutralizing Antibodies		X[b,c]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
[redacted]													

Table 20-2
Clinical Laboratory Assessments

Procedure/ Assessment	Scr (Max 6 Weeks)	Treatment Period										Study Completion	Early Termination
		Week 1	Week 4 (± 2 Days)	Week 13 (± 2 Days)	Week 26 (± 2 Days)	Week 39 (± 2 Days)	Week 52 (± 2 Days)	Week 65 (± 2 Days)	Week 78 (± 2 Days)	Week 91 (± 2 Days)	Week 104 (± 2 Days)	Week 105 (± 2 Days)	1 Weeks (± 2 Days) Post-Last Infusion
Urinalysis[f]	X												
Pregnancy Test[g]	X											X	X

Abbreviations: Scr = Screening; IgA = Immunoglobulin A; A1PI = Alpha1-proteinase inhibitor.

a. Hematology panel will consist of complete blood count [hemoglobin (Hgb), hematocrit (Hct), erythrocytes (ie, red blood cell (RBC) count), leukocytes (ie, white blood cell (WBC) count)] with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet count.

b. To be collected within 4 hours prior to the start of the IP infusion on the day of an infusion visit. Note that neutralizing antibodies will only be assayed in the case that a positive binding antibody response is recorded for the subject

c. Values obtained prior to initiation of IP treatment during Week 1 visit will serve as the baseline values.

d. Clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, phosphorus, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl-transferase (GGT), creatine phosphokinase (CPK), bilirubin (direct and total), blood urea nitrogen (BUN), uric acid, creatinine, and glucose.

e. Viral serology includes hepatitis A virus (HAV) antibody, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency type 1/2 (HIV-1/HIV-2) antibody screens, as well as parvovirus 19 (B19V) serology and nucleic acid test (NAT).

f. Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

g. For women of childbearing potential only.

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22. SUMMARY OF CHANGES

Protocol 460503 Amendment 11: 2016 JUN 21
Replaces: Amendment 10: 2016 JAN 06

In this section, changes from the previous version of the Protocol 460503 Amendment 10, dated 2016 JAN 06, are described and their rationale is given.

1. **Throughout the document**
   Description of Change: Editorial/grammatical and/or administrative changes that do not substantively affect the study conduct or patient safety have been made. Rearrangement/modifications of sections and text have been made to align with the current version of the sponsor's protocol template. Changes in the numbering of sections without substantial/major changes in the content will not be listed individually in the list of changes below.
   Purpose for Change: To comply with current protocol standards and regulatory requirements, to improve the readability and/or clarity of the protocol, to minimize redundancy, to correct typos and inconsistencies, and to reflect minor administrative/operational changes.
   Description of Change: Emphysema has been added to better define the pulmonary disease caused by severe A1PI deficiency.
   Purpose of Change: To improve the diagnostic precision of the population to be studied.

2. **Synopsis and Section 8.2. Overall Study Design**
   Description of Change: Sample size was changed from 129 subjects enrolled to 138 subjects enrolled to meet the target of 110 randomized subjects…
   Purpose for Change: Feasibility data suggest a screen failure rate of 20% instead of 15% as written in the previous version of the protocol.

3. **Section 9.3.1. Study Discontinuation Due to Disease Progression and Section 10.3.5. Early Termination Visit**
   Description of Change: Subjects who continue to show rapid progression of COPD, as determined by a decline of PD15 lung density from baseline exceeding 1.5 x the upper bound of the 95% CI of that observed in the RAPID Study… will be discontinued from the study. Subjects discontinued from study will undergo an early termination visit.
   A new literature reference was added.

Purpose of Change: To avoid continued treatment with placebo for the entire 24 months of study in subjects who show rapid progression, which is considered unethical in view of recent data (RAPID Study) showing slower decline in lung density with augmentation therapy.

4. **Synopsis and Section 9.1. Inclusion Criteria**
   Description of Change: A1PI levels for inclusion have been changed from <11 µM to < 8 µM and the requirement to perform A1PI genotyping at screening have been removed, relying instead on previously documented genotyping. The new text is shown below:
   Inclusion criterion #2. Endogenous plasma A1PI level **< 8 µM** at any time during the Screening period for treatment-naïve subjects, or following 4-weeks minimum wash-out from previous augmentation therapy in treatment-experienced subjects.
   Purpose for Change: To assure that only subjects with severe Alpha-1 PI deficiency are included in the study.
   Inclusion criterion #3. Subject has **documented** A1PI genotype of…
   Purpose for Change: To allow inclusion of subjects with documented genotypes for the listed alleles and to remove the additional genotyping at screening.

5. **Section 12.1.1.4. Unexpected Adverse Events**
   Description of Change: Text has been added to clarify the process for evaluation of expectedness of AEs.
   Purpose for Change: To comply with updated Baxalta protocol template language.

6. **Section 15.3.1 Safety Monitoring**
   Description of Change: Text has been added to describe the composition and responsibilities of the independent Data Safety Monitoring Committee.
   Purpose for Change: To comply with updated Baxalta protocol template language.

7. **Table 20-2 Clinical Laboratory Assessments**
   Description of Change: The row for genotyping has been deleted.
   Purpose for Change: To align the table with changes to the inclusion criteria described above.

INVESTIGATOR ACKNOWLEDGEMENT
PRODUCT: ARALAST NP and GLASSIA

STUDY TITLE: A Stage 1, Prospective, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Alpha$_1$-Proteinase Inhibitor (A1PI) Augmentation Therapy in Subjects with A1PI Deficiency and Chronic Obstructive Pulmonary Disease (COPD)

PROTOCOL IDENTIFIER: 460503
CLINICAL STUDY PHASE 3/4
AMENDMENT 11: 2016 JUN 21
Replaces: Amendment 10: 2016 JAN 06
ALL VERSIONS:
Amendment 10: 2016 JAN 06
Amendment 9: 2015 AUG 25
Amendment 8: 2015 APR 10
Amendment 7: 2014 DEC 18
Amendment 6: 2012 NOV 05
Amendment 5: 2012 FEB 20
Amendment 4: 2010 NOV 22
Amendment 3: 2009 AUG 20
Amendment 2: 2008 MAR 06
Amendment 1: 2006 DEC 01
Original Version: 2005 DEC 29

OTHER ID(s)
NCT Number: NCT02722304
EudraCT Number: 2015-002370-20
IND Number: IND 5170

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

_____
Signature of Coordinating Investigator Date

_____
Print Name and Title of Coordinating Investigator

_____
Signature of Sponsor Representative Date
[redacted], MD
[redacted], Global Clinical Development