

CLINICAL STUDY PROTOCOL

PRODUCT: GLASSIA

STUDY TITLE: A Phase 4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha₁-Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects

STUDY SHORT TITLE: Ph 4 GLASSIA Safety, Immunogenicity, and Bronchoalveolar Lavage Study

PROTOCOL IDENTIFIER: 471101

CLINICAL TRIAL PHASE 4

AMENDMENT 1: 2015 JAN 19
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Study Sponsor(s):	Baxter Healthcare Corporation	Baxter Innovations GmbH
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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

██████████, MD
██████████, Clinical Development
Baxter Healthcare Corporation

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.

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2. SERIOUS ADVERSE EVENT REPORTING

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

**ALL SAEs ARE TO BE REPORTED ON THE
SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND
TRANSMITTED TO THE SPONSOR
WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT**

**See 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:

- AE, Section [12.1](#)
- SAE, Section [12.1.1.1](#)
- Assessment of AEs, Section [12.1.2](#)

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3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	GLASSIA
Name of Active Ingredient	Alpha ₁ -Proteinase Inhibitor (Human)
CLINICAL CONDITION(S)/INDICATION(S)	
<ul style="list-style-type: none"> GLASSIA is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of alpha₁-proteinase inhibitor (A1PI) (also known as alpha₁-antitrypsin [AAT] deficiency). 	
PROTOCOL ID	471101
PROTOCOL TITLE	A Phase 4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha ₁ -Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects
Short Title	Ph 4 GLASSIA Safety, Immunogenicity, and Bronchoalveolar Lavage Study
STUDY PHASE	Ph 4
PLANNED STUDY PERIOD	
Initiation	Q3 2015
Primary Completion	Q3 2017
Study Completion	Q3 2017
Duration	Approximately 2 years
STUDY OBJECTIVES AND PURPOSE	
<p>Study Purpose</p> <p>The purpose of the study is two-fold: (1) to evaluate the safety and immunogenicity of GLASSIA following IV administration via in-line filtration; and, (2) to assess the effects of GLASSIA augmentation therapy on the levels of A1PI and [REDACTED] in the epithelial lining fluid (ELF) following intravenous (IV) administration at a dosage of 60 mg/kg BW/week for 25 weeks in subjects with emphysema due to congenital A1PI deficiency.</p>	
<p>Primary Objectives</p> <ol style="list-style-type: none"> To evaluate the effectiveness of the use of 5-micron in-line filter on the safety and immunogenicity of GLASSIA. To determine the effects of weekly IV augmentation therapy with GLASSIA at a dosage of 60 mg/kg body weight (BW) on antigenic and functional A1PI levels in ELF in subjects with congenital A1PI deficiency. 	
<p>Secondary Objective</p> <ol style="list-style-type: none"> To collect additional safety information for GLASSIA. 	
<p>Exploratory Objective</p> <p>[REDACTED]</p>	

STUDY DESIGN	
Study Type/ Classification/ Discipline	Safety, Immunogenicity, Efficacy
Control Type	Concurrent (active)
Study Indication Type	Treatment
Intervention Model	Parallel
Blinding/Masking	Double-blind
Study Design	<p>This Phase 4, prospective, 2-arm, double-blind, randomized, controlled, multicenter study will assess the safety, immunogenicity, and effects on the antigenic and functional A1PI levels in the ELF following GLASSIA administration via a 5-micron in-line filter at the labeled dosage of 60 mg/kg BW/week for 25 weeks in approximately 36 A1PI-deficient subjects. Subjects will be required to undergo bronchoscopy/bronchoalveolar lavage (BAL) procedures at baseline and during augmentation therapy for the evaluation of the effects of GLASSIA augmentation therapy on the levels of A1PI and ██████████ in the ELF. Once the target of 15 to 18 evaluable subjects is reached, the remaining subjects to be enrolled will be waived from undergoing the baseline and on-treatment bronchoscopy/BAL procedures. A subject will be considered evaluable only if acceptable BAL samples are obtained at both baseline and on-treatment BAL visits (see Section 20.5 and Figure 20-2 for BAL sample acceptability criteria and definition of evaluable subjects).</p> <p>A1PI-deficient subjects, who are A1PI treatment naïve or have been treated with A1PI augmentation therapy prior to study entry, will be enrolled. Subjects who are receiving or have recently been exposed to A1PI augmentation therapy at the time of study enrollment will be required to undergo an adequate washout period (minimum of 4 weeks from the time of prior A1PI treatment withdrawal) during screening. Screening A1PI measurement may be repeated due to suspected inadequate washout. During the washout period, subjects will be allowed to undergo other screening procedures for eligibility determination.</p> <p>Subjects meeting eligibility criteria will be required to undergo bronchoscopy/BAL procedures at baseline to collect BAL samples for the evaluation of the effects of GLASSIA augmentation therapy at the labeled dosage of 60 mg/kg BW/week on the levels of A1PI and ██████████ in the ELF. Subjects who have completed the baseline bronchoscopy/BAL visit and have acceptable BAL samples will be randomized in a 1:1 ratio to one of the 2 treatment arms as shown in Table 3-1. Subjects who are waived from the bronchoscopy/BAL procedures will be randomized after completing screening procedures and confirmation of eligibility (note that BAL-related eligibility criteria are not applicable for these subjects).</p>

Table 3-1 Treatment Assignments		
Treatment Arm	No. of Subjects per arm	Treatment
1	18	GLASSIA lot with particle loads representing the high end within the normal range observed in GLASSIA lots manufactured
2	18	GLASSIA lot with particle loads representing the low end within the normal range observed in GLASSIA lots manufactured

During the treatment period, all subjects will receive weekly IV infusions of GLASSIA at 60 mg/kg BW administered at a rate of 0.2 mL/kg/min for 25 weeks (ie, 25 planned infusions) via an IV administration set that includes a 5-micron in-line filter. The first infusion (Week 1), as well as infusions during Week 13 and Week 25, must be administered at the study site to facilitate monitoring and reporting of potential adverse events associated with GLASSIA infusions. 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, as acceptable per local regulations and standard practices of the study site. The infusion rate may be decreased or the infusion may be interrupted or discontinued in an individual subject in the event of intolerable moderate to severe infusion-related adverse events and/or at the discretion of the investigator.

Subjects will be asked to return to the study site every 6 weeks (ie, during Weeks 1, 7, 13, 19, and 25) for body weight measurements, as well as physical examination, vital sign measurements, and blood draw for plasma A1PI and safety laboratory sample collection, as applicable (see [Table 20.2-1](#) and [Table 20.3-1](#) for detailed list of study procedures/laboratory assessments). The on-treatment BAL visit will be conducted between Week 12 and Week 14 following initiation of GLASSIA augmentation therapy for the determination of antigenic and functional A1PI levels, as well as [REDACTED], in ELF. After completing the on-treatment BAL visit, subjects will continue to receive weekly GLASSIA infusions until Week 25 (the last infusion visit), followed by the study completion visit (Week 26) at 7 (±3) days post-last infusion.

If a subject experiences a moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation and/or lower respiratory tract infection (LRTI) during the screening period, baseline BAL visit will be postponed once in order for the subject to recover from the exacerbation (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically evident) and remain stable for at least 4 weeks after the end of exacerbation. If a moderate or severe episode of COPD exacerbation and/or LRTI occurs during the treatment phase, the subject should continue with the planned study visits and to receive weekly infusions of GLASSIA as planned, unless deemed medically inappropriate by the investigator. However, the on-treatment BAL visit will be postponed until clinical resolution of the exacerbation (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically

	evident) plus an additional minimum period of 4 weeks after the end of exacerbation.
Planned Duration of Subject Participation	The duration of each subject's participation will be approximately 8 months, including: <ul style="list-style-type: none"> • a screening period of up to 6 weeks, • a baseline period of up to 2 weeks (for subjects undergoing baseline BAL procedure), • a treatment period of 25 weeks, and • a post-treatment safety follow-up period of 7 (\pm3) days after the last infusion.
Primary Outcome Measures	
Safety	
<ol style="list-style-type: none"> 1. Number (proportion) of AEs considered potentially related to the presence of protein aggregates in the GLASSIA solution 2. Incidence of treatment-emergent adverse reactions (ARs) plus suspected ARs 3. Number (proportion) of infusions that are discontinued, slowed, or interrupted due to an AE 4. Number (proportion) of subjects who develop binding and/or neutralizing anti-A1PI antibodies 	
Efficacy	
<ol style="list-style-type: none"> 1. Antigenic A1PI levels in ELF 2. Functional A1PI (also known as anti-neutrophil elastase capacity [ANEC]) levels in ELF 	
Secondary Outcome Measures	
Safety	
<ol style="list-style-type: none"> 1. Incidence of treatment-emergent adverse events (AEs) 2. Number (proportion) of subjects who experienced a shift from normal or clinically insignificant abnormal laboratory values at baseline to clinically significant abnormal laboratory values 3. Number (proportion) of subjects with treatment-emergent seroconversion or positive nucleic acid test (NAT) for parvovirus B19 (B19V) 	
Exploratory Outcome Measures	
<p>██████████</p> <p>██████████</p> <p>██████████</p> <p>██████████</p> <p>██████████</p>	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	GLASSIA Dose: 60 mg/kg BW Dosage form: Injection, solution Dosage frequency: Weekly Mode of Administration: Intravenous

SUBJECT SELECTION	
Targeted Accrual	Enrollment will be closed when both conditions are met: (a) At least 15 evaluable subjects with acceptable BAL samples collected from both the baseline and on-treatment BAL visits have been achieved (b) A minimum of 36 subjects have been randomized.
Number of Groups/Arms/Cohorts	2
Inclusion Criteria A subject must meet ALL of the following criteria to be eligible for inclusion in this study: <ol style="list-style-type: none"> 1. Male or female 18 years of age or older at the time of screening. 2. A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, or Pi*Null/Null. 3. Endogenous circulating A1PI level of <8 µM (A1PI measurement may be repeated for subjects with an initial screening A1PI level of 8 µM or above that is suspected to be due to inadequate washout of prior A1PI therapy). 4. Subject must have at least one of the following: clinical diagnosis of emphysema, evidence of emphysema on computerized tomography (CT) scan of the chest within 52 weeks of screening, and/or evidence of airway obstruction which is not completely reversed with bronchodilator treatment at the time of screening. 5. No clinically significant abnormalities detected on a 12-lead electrocardiogram (ECG) performed at the time of screening (ECG obtained within 26 weeks prior to screening may be used, if available). 6. No clinically significant abnormalities (other than emphysema and chronic bronchitis) detected on chest X-ray at the time of screening (chest X-ray or CT scan obtained within 52 weeks prior to screening may be used, if available). 7. If the subject is being treated with any respiratory medications including inhaled bronchodilators, inhaled anticholinergics, inhaled corticosteroids, or low-dose systemic corticosteroids (prednisone ≤10 mg/day or its equivalent), the doses of the subject's medications have remained unchanged for at least 14 days prior to screening. 8. The subject is a nonsmoker or has ceased smoking for a minimum of 13 weeks prior to screening (serum cotinine level at screening within normal range of a nonsmoker) and agrees to refrain from smoking throughout the course of the study. 9. If female of childbearing potential, the subject presents with a negative pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study. 10. The subject is willing and able to comply with the requirements of the protocol. 	
Exclusion Criteria A subject who meets ANY of the following criteria is NOT eligible for this study: <ol style="list-style-type: none"> 1. The subject is experiencing or has a history of clinically significant pulmonary disease other than COPD/emphysema and/or chronic bronchitis. 2. The subject is experiencing or has a history of cor pulmonale. 3. The subject has moderate or severe bronchiectasis, defined as total daily sputum production of >10 mL. 4. The subject has a history of frequent pulmonary exacerbations (greater than 2 moderate or severe exacerbations within 52 weeks prior to screening). 5. The subject is experiencing a pulmonary exacerbation at the time of screening (subject may be re-screened 4 weeks after the clinical resolution of an exacerbation). 	

6. The subject has clinically significant congestive heart failure, with New York Heart Association (NYHA) Class III/IV symptoms.
7. The subject is experiencing an active malignancy or has a history of malignancy within 5 years prior to screening, with the exception of the following: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or stable prostate cancer not requiring treatment.
8. The subject has a history of lung or any other organ transplant, is currently on a transplant list, or has undergone major lung surgery.
9. The subject is receiving long-term oxygen supplementation (other than on a short-term basis for acute COPD exacerbation, or supplemental O₂ with continuous positive airway pressure [CPAP], or bi-level positive airway pressure [BiPAP]).
10. Known history of hypersensitivity following infusions of human blood or blood components.
11. Immunoglobulin A (IgA) deficiency (<8 mg/dL at screening).
12. Abnormal clinical laboratory results obtained at the time of screening meeting any of the following criteria:
 - a. Serum alanine aminotransferase (ALT) >3.0 times upper limit of normal (ULN)
 - b. Serum total bilirubin >2.0 times ULN
 - c. >2+ proteinuria on urine dipstick analysis
 - d. Serum creatinine >2.0 times ULN
 - e. Absolute neutrophil count (ANC) <1500 cells/mm³
 - f. Hemoglobin (Hgb) <9.0 g/dL
 - g. Platelet count <100,000/mm³
13. Known history of OR positive serological evidence at the time of screening for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection.
14. The subject has any clinically significant medical, psychiatric, or cognitive illness, or any other uncontrolled medical condition (eg, unstable angina, transient ischemic attack) that, in the opinion of the investigator, would impede the subject's ability to comply with the study procedures, pose increased risk to the subject's safety, or confound the interpretation of study results.
15. The subject has participated in another clinical study involving an investigational product (other than A1PI) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an investigational product or device during the course of this study.
16. The subject is a family member or employee of the investigator.
17. If female, the subject is nursing at the time of screening.

Additional Inclusion Criterion for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures

1. The subject must have pulmonary functions at screening meeting both of the following:
 - a. Post-bronchodilator forced expiratory volume in 1 second (FEV₁) ≥50%
 - b. If FEV₁ is >80% predicted, then FEV₁/forced vital capacity (FVC) must be <0.7 and/or DL_{CO} must be ≥30% and ≤65% predicted.

Additional Exclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures

1. The subject has contraindication(s) to bronchoscopy or high risk factors, such as recent myocardial infarction, active myocardial ischemia, other cardiopulmonary instability, tracheal obstruction or stenosis, moderate to severe hypoxemia or any degree of hypercapnia, unstable asthma, uremia, pulmonary hypertension, severe hemorrhagic diathesis, and cervical C1/C2 arthritis.
2. The subject has had lung surgery which may interfere with bronchoscopy.
3. Known history of allergic/hypersensitivity reactions to medications used during and for perioperative care associated with the bronchoscopy/BAL procedures, such as local anesthetics, sedatives, pain control medications.
4. The subject is receiving and requires long-term (>4 weeks) immunosuppressive therapy, such as systemic corticosteroids at doses greater than 10 mg/day of prednisone (or its equivalent), mycophenolate mofetil, azathioprine, cyclophosphamide, and rituximab.
5. If a subject is receiving anticoagulant or anti-platelet therapy (such as warfarin and clopidogrel), the subject is unwilling to or unable to safely discontinue anticoagulant or anti-platelet therapy within 7 days prior to until at least 24 hours after the BAL procedures. An exception is low-dose aspirin alone which is allowed.

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size calculation for the BAL component of the study was based on the natural log transformed primary endpoint data, ELF antigenic A1PI level (nM), generated during Baxter's Clinical Study 460502. In Clinical Study 460502, a mean difference from pre- to post-treatment in ELF antigenic A1PI of 1.32 with standard deviation of 0.96 on natural log scale was observed. Using this variance estimate, a sample size of 15 evaluable subjects should be sufficient to detect a mean difference in the natural log transformed ELF antigenic A1PI of approximately 0.87 with 90% power, using a paired t-test and a one-sided significance level of 0.025.

A sample size of 15 evaluable subjects will also be sufficient to detect a mean difference in the natural log transformed ELF functional A1PI (ANEC) of approximately 1.04, with 90% power, assuming a standard deviation in the differences between pre- and post-treatment ANEC values to be 20% higher than that for antigenic A1PI.

Based on the experience from Clinical Study 460502, it is estimated that approximately 26 to 32 subjects will be needed in order to achieve 15 to 18 BAL evaluable subjects, respectively. Thus, an overall study enrollment target of 36 subjects should be adequate to meet the target sample size for the BAL component of the study.

Planned Statistical Analysis

ELF antigenic and functional A1PI levels, as well as changes from baseline, will be summarized descriptively and displayed graphically (data permitting) based on data pooled across both treatment arms. These changes will be analyzed in one-sided paired t-tests at an alpha level of 0.025.

Plasma trough antigenic and functional A1PI levels, as well as changes from baseline, will be summarized descriptively and displayed graphically (data permitting) based on data pooled across both treatment arms. Plasma antigenic and functional A1PI levels obtained at the baseline and on-treatment BAL visits will be summarized separately and, data permitting, to be correlated with the corresponding values in the ELF.

[REDACTED]

Changes from baseline in ELF and plasma antigenic and functional A1PI levels, as well as [REDACTED], will be summarized in the following subgroups: by sex, age (≤ 65 , >65), race, and ethnicity.

[REDACTED]

The safety outcome measures, including AEs of interest that may be immune-mediated, treatment-emergent ARs plus suspected ARs (see Section 12.1.1.3 for definitions), and treatment-emergent incidence of immunogenicity and seroconversion, will be summarized descriptively with 95% confidence intervals (CIs) as appropriate. In the event of any clinically significant trends in treatment-emergent AE(s) of interest, further analysis including potential correlation with the presence of particulates in the GLASSIA solution will be performed. In the event of treatment-emergent immunogenicity, any potential temporal relationship of anti-A1PI antibody formation with the occurrence of potentially immune-mediated AEs will be examined. Additionally, in the event of any clinically significant trends in treatment-emergent AE(s) of interest, further analysis including potential correlation with the presence of particulates in the GLASSIA solution will be performed.

Any clinically significant laboratory values that are considered as clinically significant by the investigator (ie, reported as AEs), as well as in accordance with the thresholds provided in Section 20.4, will be analyzed and reported, including shift tables.

Safety parameters will be summarized descriptively by sex, age (≤ 65 , >65), race, and ethnicity. No hypothesis tests are planned; however, [REDACTED]

[REDACTED]

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	Degree Celsius
°F	Degree Fahrenheit
AIPI	Alpha ₁ -Proteinase Inhibitor
AAT	Alpha ₁ -antitrypsin
AE/AEs	Adverse event/adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANEC	Anti-neutrophil elastase capacity
APE	Acute pulmonary exacerbation
AR/ARs	Adverse reaction/adverse reactions
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
B19V	Parvovirus B19
BiPAP	Bi-level positive airway pressure
BUN	Blood urea nitrogen
BW	Body weight
C3	Complement component 3
C4	Complement component 4
CFR	Code of Federal Regulations
CH50	50% hemolytic complement activity of serum
CI	Confidence intervals
cm	Centimeter(s)
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF(s)	Case Report Form(s)
CT	Computerized tomography
dL	Deciliter(s)
DL _{CO}	Diffusing Capacity of Carbon Monoxide
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram

Abbreviation	Definition
EDTA	Ethylenediaminetetraacetic acid
ELF	Epithelial lining fluid
EP	European Pharmacopeia
ERS	European Respiratory Society
FAS	Full analysis set
FDA	United States Food and Drug Administration
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
HAV	Hepatitis A virus
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
HEV	Hepatitis E virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hpf	High power field
ICF	Informed consent form
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
in	Inch(es)
IP	Investigational product
IRT	Interactive response technology
IV	Intravenous
IWRS	Interactive Web Response System
kD	Kilodalton(s)
kg	Kilogram(s)
lb	Pound(s)
LDH	Lactic dehydrogenase
LRT	Lower respiratory tract
LRTI	Lower respiratory tract infection
μM	Micromolar
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mg	Milligram(s)
min	Minute (s)
mL	Milliliter(s)
mm ³	Cubic millimeter
mm Hg	Millimeter(s) of mercury
NAT	Nucleic acid test
NE	Neutrophil elastase
nM	Nanomolar(s)
NMC	Non-medical complaint
NYHA	New York Heart Association
O ₂	Oxygen
PCR	Polymerase chain reaction
PP	Per protocol
ppm	Parts per million
RBC	Red blood cell
SAE	Serious adverse event
SAER	Serious adverse event report
S/D	Solvent/detergent
SIC	Subject identification code
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	White blood cell

6. BACKGROUND INFORMATION

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

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.^{2;3} Individuals with a severe deficiency are defined as those with serum A1PI levels less than 35% of the average normal level,^{4;5} or less than 11 μM .^{6;7;8} Severely affected individuals may have no detectable A1PI protein in their serum. 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.⁹ In clinical practice, majority (96%) of A1PI deficiency related diseases are linked to Pi*ZZ genotype, with the remaining 4% to Pi*SZ and other rare or null genotypes.

Individuals with Pi*ZZ show a significant intracellular polymerization of their A1PI in the liver, often resulting in liver damage with a variable clinical presentation. In addition, the profound suppression of A1PI secretion into the systemic circulation significantly increases the risk of developing panacinar emphysema.¹⁰ The threshold level of A1PI in the lower respiratory tract (LRT) needed to provide clinical benefit is not known; however, emphysema in A1PI-deficient subjects has been thought to develop because the level of A1PI in the LRT is insufficient to inhibit serine proteases. Serine proteases, such as NE, are present in the LRT in higher than normal concentrations as a result of inflammation or infection.¹¹ If left unchecked, due to insufficient A1PI, the proteolytic activity of these proteases can destroy the connective tissue framework of the lung parenchyma.^{12;13}

Therapy for A1PI-deficient subjects is directed towards replacement or augmentation of serum A1PI levels.^{14;15;16;17;18;19;20;21;22} This therapy is based on the concept that an increase in the serum level of A1PI 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.^{23;24} Wewers *et al.* showed that, at steady-state, augmentation therapy with once a week dosing of A1PI (60 mg/kg body weight [BW]/week) resulted in trough circulating A1PI levels to $>11 \mu\text{M}$ in subjects with A1PI deficiency of Pi*Z/Z genotype.²⁵

Historically, it was believed that 11 μM is the protective threshold level, based on the assumption that subjects with Pi*Z/Z, Pi*Null/Null, or Pi*Z/Null genotypes had severe A1PI deficiency (circulating A1PI levels below 11 μM) and emphysema; whereas subjects with Pi*S/Z genotype, who at that time were considered to have an average A1PI level of 11 μM , were protected from emphysema.

GLASSIA is the only sterile, ready-to-use, liquid preparation of purified human A1PI indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of A1PI. The product was approved by the US Food and Drug Administration (FDA) in 2010, on the basis of safety and biochemical demonstration in a Phase I dose-escalation and a Phase II/III pivotal clinical trial in a total of 65 individual subjects with severe A1PI deficiency.

The clinical lots used in the GLASSIA Phase II/III trial contained small amounts of visible protein particulates which were aggregates of the A1PI. Protein aggregation is a known phenomenon with protein therapeutics and has been shown to be present in active comparator used in the Phase II/III trial, as well as other commercially available A1PI products upon reconstitution of the lyophilized powder. During the Phase II/III clinical trial, no safety signals of concern were reported. The most common adverse reactions (ARs) (>0.5% of infusions) reported were headache and upper respiratory tract infection. These adverse events (AEs) were consistent with those reported for the other licensed A1PI products. Potential immunogenicity following repeated administration of GLASSIA was evaluated in the Phase II/III trial, where 50 subjects received weekly infusions of either GLASSIA or PROLASTIN (active comparator) from Week 1 to Week 12 and then weekly infusions of GLASSIA (all subjects) from Week 13 to Week 24. Immunogenicity was monitored at baseline, Week 12, and Week 24. All samples were negative for the presence of anti-A1PI antibodies, with the exception of a single sample (Week 12) with a low titer of 2 in one subject. The Week 24 sample from this subject was negative, suggesting a low level, transient immunogenic response. Nevertheless, as an added precautionary measure, it is recommended that GLASSIA be filtered twice before product administration: through a 5 micron filter needle during product pooling and then through a 5 micron in-line filter during product administration (see GLASSIA package insertⁱ).

The effectiveness of the in-line filtration procedure in removing visible and subvisible particles in GLASSIA was examined in a recent in vitro study. Four GLASSIA lots were

ⁱ Baxter Healthcare Corporation. Product label: GLASSIA [Alpha1-Proteinase Inhibitor (Human)].
March 2014.

chosen to represent the high and low ends of the range of particle counts normally observed for GLASSIA manufactured. (Note that all GLASSIA lots must meet the requirements for visible and subvisible particulates set forth by the United States Pharmacopeia [USP] and the European Pharmacopeia [EP] prior to release for use in humans). The use of a 5-micron in-line filter has been shown to effectively remove visible particles (from several to >10 particles in unfiltered solution to no more than 2 particles per 50-mL vial after filtration) and subvisible particles (by 12- to 76-fold for particles across all particle size categories ranging from 2 to >100 micron) (data on file). In fact, the 5-micron in-line filter is also effective in reducing the number of particles that are smaller (2 to 5-micron in diameter) than the nominal 5-micron pore-size of the filter from an average of 23227 to 489 particles per 50-mL vial, representing a 49-fold reduction. The filtration process did not alter the A1PI potency, as demonstrated by a lack of difference in the elastase inhibitory activity measurements in unfiltered and filtered GLASSIA solution.

Nevertheless, given a lack of clear understanding and the paucity of direct clinical evidence correlating parenteral administration of protein aggregates to clinical AEs and risk of immunogenicity, there have been theoretical concerns about protein aggregates in a therapeutic product on the safety risks to humans. To address these concerns, a key goal of this study is to evaluate the clinical safety profile of GLASSIA with focus on AEs of interest that have been suggested to be potentially associated with protein aggregates and visible/subvisible particles, such as pulmonary embolism particularly of non-thrombotic or microvascular origin, unexplained chest pain, dyspnea, or cardiopulmonary arrest of non-cardiac etiology, interstitial pneumonitis, injection site reactions, granuloma, hypersensitivity or anaphylactic reactions, and immunogenicity incidence. GLASSIA lots containing particles of ≥ 2 micron in diameter representative of the high and low ends of the range normally observed in GLASSIA manufacturing will be selected for evaluation in this study. All GLASSIA administrations will follow the 2-step filtration process (through a 5 micron filter needle during product pooling and then through a 5 micron in-line filter during product administration) as outlined in the GLASSIA package insert.

The second goal of this study is to obtain additional safety data, and to evaluate the effects of GLASSIA augmentation therapy on the levels of A1PI and [REDACTED] in the ELF following weekly intravenous (IV) augmentation therapy with GLASSIA in subjects with emphysema due to congenital A1PI deficiency. In the pivotal Ph II/III study, there were fewer subjects (7 subjects in the GLASSIA group and 2 subjects in the active comparator group) than planned (15 subjects) having ELF analyte results available for evaluation. Additionally, effect of GLASSIA augmentation therapy on ELF functional

A1PI (ie, anti-neutrophil elastase capacity [ANEC]) could not be examined due to missing data. Thus, this study is designed to include bronchoscopy/bronchoalveolar lavage (BAL) visits to collect data for the assessments of change from baseline in the antigenic and functional A1PI levels, as well as [REDACTED], in the ELF following 13 weeks of weekly IV administration of GLASSIA at the approved dose of 60 mg/kg BW.

6.1 Description of Investigational Product

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 specific activity of GLASSIA is at least 0.7 mg functional A1PI per mg of total protein (the specific activity of a particular lot will be provided in the certificate of analysis). The product is clear and colorless to yellow-green and may contain a few particles (ie, protein filaments).

GLASSIA supplied in the US is prepared from human plasma obtained from US-licensed plasma collection centers by a modified version of the cold ethanol fractionation process and the A1PI is then purified using chromatographic methods. GLASSIA does not contain stabilizers or any other added substances (such as sucrose, albumin or mannitol). GLASSIA contains no preservatives and no latex.

Further information can be found in the GLASSIA package insert.

6.1.1 Rationale for the Selection of Dosing Regimen

The dosing regimen of GLASSIA chosen for this study, 60 mg/kg given intravenously once per week, is the standard FDA-approved dosing regimen for GLASSIA, as well as all other plasma-derived A1PI products in the same class. At this dosage, GLASSIA has been demonstrated to be safe and well tolerated in a total of 65 subjects with congenital A1PI-deficiency, and was shown to increase and maintain circulating trough antigenic and functional A1PI levels to 14.7 μM (median; range: 11.6-18.5 μM) and 11.9 μM (median; range: 8.2-16.9 μM), respectively (see GLASSIA package insert).

6.1.2 Rationale for the Selection of Route of Administration and Infusion Rate

The route of administration (intravenous infusion), as well as the infusion rate (0.2 mL/kg BW/min), selected for this study are in accordance with the FDA-approved package insert.

6.2 Clinical Condition/Indication

GLASSIA is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of A1PI (AAT deficiency).

6.3 Population To Be Studied

Subjects with severe congenital A1PI-deficiency (endogenous A1PI level $<8 \mu\text{M}$ with genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, or Pi*Null/Null) and emphysema are planned for enrollment into this study.

6.4 Findings From Nonclinical and Clinical Studies

6.4.1 Summary of Nonclinical Data

GLASSIA was evaluated in two single dose general toxicology studies in Sprague-Dawley rats and New Zealand White rabbits, and one repeated dose study in New Zealand White rabbits.

In single dose studies, a single dose of 0, 60 and 600 mg/kg (rabbits) or 640 mg/kg (rats) was administered intravenously and the animals were observed for 14 days. There were no changes in body weight, clinical chemistry, hematology and gross pathology that could be attributed to GLASSIA administration.

In the repeated dose study, New Zealand White rabbits received GLASSIA (300 mg/kg) once daily for five consecutive days. Animals were monitored for changes in clinical signs, body weight, clinical chemistry, hematology, necropsy and histopathology on Day 1 or 14 after the last administration. A minor increase in group mean neutrophils was measured on Day 1 after the last GLASSIA administration. Recovery was observed after 14 days.

Long-term studies in animals to evaluate carcinogenesis, mutagenesis or impairment of fertility have not been conducted.

Animal reproduction studies have not been conducted with GLASSIA.

No toxicological effects due to the solvent/detergent reagents, tri-(n)-butyl phosphate, and polysorbate 80 (Tween 80), used in the virus inactivation procedure are expected since the residual levels are less than 5 and 20 ppm, respectively.

6.4.2 Summary of Clinical Data

Findings from clinical studies are provided in the GLASSIA package insert.

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

Transmission of blood-borne diseases is a theoretical risk since GLASSIA is derived from pooled human plasma. To decrease the potential contamination with blood-borne viruses, stringent procedures have been employed in the manufacture of this product from the screening of plasma donors through plasma collection and preparation. To further reduce the risk of viral transmission, the manufacturing process includes two steps of viral removal or inactivation: (1) treatment with a solvent/detergent (S/D) mixture of tri-n-butyl phosphate and polysorbate 80 (Tween 80) which inactivates enveloped viral agents such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV); and, (2) a nanofiltration step through a 15 nm filter which can remove both enveloped and non-enveloped viral agents (such as hepatitis A virus [HAV]). *In vitro* virus clearance studies demonstrated a virus log reduction factor of 4 or greater. To date, no seroconversion for hepatitis B or C (HBV or HCV) or human immunodeficiency virus (HIV) or any other known infectious agent have been reported with the use of GLASSIA during the clinical studies.

GLASSIA is contraindicated in subjects with a history of anaphylactic or severe hypersensitivity reactions to human A1PI preparations.

GLASSIA may contain trace amounts of immunoglobulin A (IgA). GLASSIA is contraindicated in subjects with known antibodies to IgA, and in subjects with selective or severe IgA deficiency who may develop anti-IgA antibodies that can result in severe hypersensitivity and anaphylactic reactions. IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, THE INFUSION MUST BE DISCONTINUED IMMEDIATELY. Epinephrine, antihistamines, and other appropriate supportive therapy should be available for the treatment of any acute anaphylactic or anaphylactoid reactions.

6.6 Compliance Statement

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

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is two-fold: (1) to evaluate the safety and immunogenicity of GLASSIA following IV administration via in-line filtration; and, (2) to assess the effects of GLASSIA augmentation therapy on the levels of A1PI and [REDACTED] in the ELF following IV administration at a dosage of 60 mg/kg BW/week for 25 weeks in subjects with emphysema due to congenital A1PI deficiency.

7.2 Primary Objectives

1. To evaluate the effectiveness of the use of 5-micron in-line filter on the safety and immunogenicity of GLASSIA.
2. To determine the effects of weekly IV augmentation therapy with GLASSIA at a dosage of 60 mg/kg BW on antigenic and functional A1PI levels in ELF in subjects with congenital A1PI deficiency.

7.3 Secondary Objective

- To collect additional safety information for GLASSIA.

7.4 Exploratory Objective

[REDACTED]

8. STUDY DESIGN

8.1 Brief Summary

This Phase 4, prospective, 2-arm, double-blind, randomized, controlled, multicenter study will assess the safety, immunogenicity, and effects on the antigenic and functional A1PI levels in the ELF following GLASSIA administration via a 5-micron in-line filter at the labeled dosage of 60 mg/kg BW/week for 25 weeks in A1PI-deficient subjects who are A1PI-treatment naïve, who are currently receiving A1PI treatment at the time of enrollment, or who have previously received A1PI treatment.

8.2 Study Design

A1PI-deficient subjects, who are A1PI treatment naïve or have previously been treated with A1PI augmentation therapy, will be enrolled. Subjects who are receiving or have recently been exposed to A1PI augmentation therapy at the time of study enrollment will be required to undergo an adequate washout period (minimum of 4 weeks from the time

of prior A1PI treatment withdrawal) during screening. Screening A1PI measurement may be repeated due to suspected inadequate washout. During the washout period, subjects will be allowed to undergo other screening procedures for eligibility determination.

Subjects meeting eligibility criteria will be required to undergo bronchoscopy/BAL procedures at baseline and following IP treatment for the evaluation of the effects of GLASSIA augmentation therapy at the labeled dosage of 60 mg/kg BW/week on the levels of A1PI and ██████████ in the ELF. Once the target of 15 to 18 evaluable subjects is reached, the remaining subjects to be enrolled will be waived from undergoing the baseline and on-treatment bronchoscopy/BAL procedures. A subject will be considered evaluable only if acceptable BAL samples are obtained at both baseline and on-treatment BAL visits (see Section 20.5 and Figure 20-2 for BAL sample acceptability criteria and definition of evaluable subjects).

Enrollment will be closed when both conditions are met:

- (a) At least 15 evaluable subjects with acceptable BAL samples collected from both the baseline and on-treatment BAL visits
- (b) At a minimum of an overall 36 randomized subjects.

If for any reasons the target of at least 15 evaluable subjects have not been attained with initial 36 randomized subjects, additional subjects will be enrolled to achieve the BAL enrollment target.

Subjects who have completed the baseline bronchoscopy/BAL visit and have acceptable BAL samples will be randomized in a 1:1 ratio to one of the 2 treatment arms as shown in Table 8-1. Subjects who are waived from the bronchoscopy/BAL procedures will be randomized after completing screening procedures and confirmation of eligibility (note that BAL-related eligibility criteria are not applicable for these subjects).

Treatment Arm	No. of Subjects Per Arm	Treatment
1	18	GLASSIA lot with particle loads representing the high end within the normal range observed in GLASSIA lots manufactured
2	18	GLASSIA lot with particle loads representing the low end within the normal range observed in GLASSIA lots manufactured

During the treatment period, subjects in both treatment arms will receive weekly IV infusions of GLASSIA at 60 mg/kg BW administered at a rate of 0.2 mL/kg/min for 25 weeks (ie, 25 planned infusions) via an IV administration set that includes a 5-micron in-line filter. The first infusion (Week 1), as well as infusions during Week 13 and Week 25, must be administered at the study site to facilitate monitoring and reporting of potential AEs associated with GLASSIA infusions. 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, as acceptable per local regulations and standard practices of the study site.

Subjects will be asked to return to the study site every 6 weeks (ie, during Weeks 1, 7, 13, 19, and 25) for body weight measurements, as well as physical examination, vital sign measurements, and blood draw for plasma A1PI and safety laboratory sample collection, as applicable (see [Table 20.2-1](#) and [Table 20.3-1](#) for detailed list of study procedures/laboratory assessments). The on-treatment BAL visit will be conducted between Week 12 and Week 14 following initiation of GLASSIA augmentation therapy for the determination of antigenic and functional A1PI levels, as well as ██████████ ██████████ in ELF. After completing the on-treatment BAL visit, subjects will continue to receive weekly GLASSIA infusions until Week 25 (the last infusion visit), followed by the study completion visit (Week 26) at 7 (± 3) days post-last infusion.

The overall study design is illustrated in [Figure 20-1](#) (Supplement 20.1).

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study will be approximately 2 years from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be approximately 16 months.

- The duration of each subject's participation from enrollment to subject completion (ie, last study visit) is anticipated to be approximately 8 months (including a screening period of up to 6 weeks, a baseline period of up to 2 weeks [for subjects undergoing baseline BAL procedure], a treatment period of 25 weeks, and a post-treatment safety follow-up period of 7 [± 3] days of after the last infusion), unless the subject withdraws or is prematurely discontinued from the study.

8.4 Outcome Measures

8.4.1 Primary Outcome Measures

Safety

1. Number (proportion) of AEs considered potentially related to the presence of protein aggregates in the GLASSIA solution
2. Incidence of treatment-emergent ARs plus suspected ARs
3. Number (proportion) of infusions that are discontinued, slowed, or interrupted due to an AE
4. Number (proportion) of subjects who develop binding and/or neutralizing anti-A1PI antibodies

Efficacy

1. Antigenic A1PI levels in ELF
2. Functional A1PI (also known as ANEC) levels in ELF

8.4.2 Secondary Outcome Measures

Safety

1. Incidence of treatment-emergent AEs
2. Number (proportion) of subjects who experienced a shift from normal or clinically insignificant abnormal laboratory values at baseline to clinically significant abnormal laboratory values
3. Number (proportion) of subjects with treatment-emergent seroconversion or positive viral nucleic acid test (NAT) for parvovirus B19 (B19V)

8.4.3 Exploratory Outcome Measures

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.5 Randomization and Blinding

This is a 2-arm, double-blind, randomized, controlled clinical study. In order to minimize/avoid bias, subjects meeting all eligibility criteria (Section 9.1 through Section 9.4) will be randomly assigned to 1 of 2 treatment arms at a ratio of 1:1. Note that randomization is to take place only after the subject has successfully completed the baseline BAL visit with verification of having evaluable BAL samples collected. For those subjects to be enrolled after the target of at least 15 evaluable BAL subjects have been achieved and thus exempted from BAL procedures, randomization will take place upon confirmation of the main study eligibility criteria (Section 9.1 and Section 9.2) being met.

Randomization codes will be generated and maintained by an Interactive Response Technology (IRT) via an Interactive Web Response System (IWRS). Treatment assignment will not be revealed to the subject, investigators, study site personnel or the sponsor, except for unblinded study personnel such as the unblinded pharmacist directly involved in the preparation of infusion solutions, the unblinded study monitor(s), and the unblinded biostatistician. The pharmacist preparing the infusion solution will be able to access the randomization codes and will be responsible for maintaining any unblinded pharmacy records in a secure, access-controlled location.

8.5.1 Unblinding Procedures at Study Sites

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

The study may be terminated by the sponsor in the event of unexpected safety or medical concerns. Specific stopping rules will not be established for this study, as GLASSIA is an approved product with a demonstrated record of safety at the approved dosage of 60 mg/kg BW/week which is to be employed in this study.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

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

Dosage Form: Injection, solution

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

Storage: GLASSIA must be stored at 2-8 °C (36 to 46 °F). Do not freeze the product. Do not use past the expiration date.

8.7.2 Preparation of Infusion Solution

The dose (in mg) will be calculated based on the subject's individual body weight at screening. The same dose (in mg) is to be administered to an individual subject throughout the course of treatment. Adjustment based on body weight changes during the course of the study is not planned; however, dose (in mg) may be adjusted if deemed medically necessary at the discretion of the investigator (eg, body weight change by >10%). Only body weight measurements taken using standardized procedures during study visits (Weeks 1, 7, 13, 19, or 25) will be used for dose calculations.

The volume of infusion solution (in mL) will be calculated based on the content of functional A1PI (potency) in GLASSIA vials, as specified in the certificate of analysis to be provided with a particular GLASSIA lot and as printed on the product carton and vial.

For instructions for the preparation and administration of GLASSIA infusion solution, please refer to the GLASSIA package insert.

8.7.3 Administration

GLASSIA is for intravenous use only.

Route of administration: IV infusion via a 5-micron in-line filter

Rate of administration: 0.2 mL/kg BW/min

(The rate of infusion will be regulated by an ambulatory infusion pump.)

8.7.4 Description of Treatment

Treatment: GLASSIA [Alpha₁-Proteinase Inhibitor (Human)]

Dose: 60 mg/kg BW/week

Dosage frequency: Once every week (\pm 2 days)

Treatment period: 25 weeks (ie, 25 planned infusions), to be followed by a 7 (\pm 3 days) post-treatment safety follow-up period

8.7.5 Investigational Product Accountability

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

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

A subject must meet ALL of the following criteria to be eligible for inclusion in this study:

1. Male or female 18 years of age or older at the time of screening.
2. A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, Pi*Null/Null.
3. Endogenous circulating A1PI level of <8 μM (A1PI measurement may be repeated for subjects with an initial screening A1PI level of 8 μM or above that is suspected to be due to inadequate washout of prior A1PI therapy).
4. Subject must have at least one of the following: clinical diagnosis of emphysema, evidence of emphysema on computerized tomography (CT) scan of the chest within 52 weeks of screening, and/or evidence of airway obstruction which is not completely reversed with bronchodilator treatment at the time of screening.
5. No clinically significant abnormalities detected on a 12-lead electrocardiogram (ECG) performed at the time of screening (ECG obtained within 26 weeks prior to screening may be used, if available).
6. No clinically significant abnormalities (other than emphysema and chronic bronchitis) detected on chest X-ray at the time of screening (chest X-ray or CT scan obtained within 52 weeks prior to screening may be used, if available).
7. If the subject is being treated with any respiratory medications including inhaled bronchodilators, inhaled anticholinergics, inhaled corticosteroids, or low-dose systemic corticosteroids (prednisone ≤ 10 mg/day or its equivalent), the doses of the subject's medications have remained unchanged for at least 14 days prior to screening.
8. The subject is a nonsmoker or has ceased smoking for a minimum of 13 weeks prior to screening (serum cotinine level at screening within normal range of a nonsmoker) and agrees to refrain from smoking throughout the course of the study.
9. If female of childbearing potential, the subject presents with a negative pregnancy test at screening and agrees to employ adequate birth control measures for the duration of the study.
10. The subject is willing and able to comply with the requirements of the protocol.

9.2 Exclusion Criteria

A subject who meets ANY of the following criteria is NOT eligible for this study:

1. The subject is experiencing or has a history of clinically significant pulmonary disease other than COPD/emphysema and/or chronic bronchitis.
2. The subject is experiencing or has a history of cor pulmonale.
3. The subject has moderate or severe bronchiectasis, defined as total daily sputum production of >10 mL.
4. The subject has a history of frequent pulmonary exacerbations (greater than 2 moderate or severe exacerbations within 52 weeks prior to screening).
5. The subject is experiencing a pulmonary exacerbation at the time of screening (subject may be re-screened 4 weeks after the clinical resolution of an exacerbation).
6. The subject has clinically significant congestive heart failure, with New York Heart Association (NYHA) Class III/IV symptoms.
7. The subject is experiencing an active malignancy or has a history of malignancy within 5 years prior to screening, with the exception of the following: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or stable prostate cancer not requiring treatment.
8. The subject has a history of lung or any other organ transplant, is currently on a transplant list, or has undergone major lung surgery.
9. The subject is receiving long-term oxygen supplementation (other than on a short-term basis for acute COPD exacerbation, or supplemental O₂ with continuous positive airway pressure [CPAP], or bi-level positive airway pressure [BiPAP]).
10. Known history of hypersensitivity following infusions of human blood or blood components.
11. Immunoglobulin A (IgA) deficiency (<8 mg/dL at screening).
12. Abnormal clinical laboratory results obtained at the time of screening meeting any of the following criteria:
 - a. Serum alanine aminotransferase (ALT) >3.0 times upper limit of normal (ULN)
 - b. Serum total bilirubin >2.0 times ULN
 - c. >2+ proteinuria on urine dipstick analysis
 - d. Serum creatinine >2.0 times ULN
 - e. Absolute neutrophil count (ANC) <1500 cells/mm³
 - f. Hemoglobin (Hgb) <9.0 g/dL
 - g. Platelet count <100,000/mm³

13. Known history of OR positive serological evidence at the time of screening for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) Type 1/2 infection.
14. The subject has any clinically significant medical, psychiatric, or cognitive illness, or any other uncontrolled medical condition (eg, unstable angina, transient ischemic attack) that, in the opinion of the investigator, would impede the subject's ability to comply with the study procedures, pose increased risk to the subject's safety, or confound the interpretation of study results.
15. The subject has participated in another clinical study involving an investigational product (other than A1PI) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an investigational product or device during the course of this study.
16. The subject is a family member or employee of the investigator.
17. If female, the subject is nursing at the time of screening.

9.3 Additional Inclusion Criterion for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures

1. The subject must have pulmonary functions at screening meeting both of the following:
 - a. Post-bronchodilator forced expiratory volume in 1 second (FEV_1) $\geq 50\%$
 - b. If FEV_1 is $>80\%$ predicted, then FEV_1 /forced vital capacity (FVC) must be <0.7 and/or DL_{CO} must be $\geq 30\%$ and $\leq 65\%$ predicted.

9.4 Additional Exclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures

1. The subject has contraindication(s) to bronchoscopy or high risk factors, such as recent myocardial infarction, active myocardial ischemia, other cardiopulmonary instability, tracheal obstruction or stenosis, moderate to severe hypoxemia or any degree of hypercapnia, unstable asthma, uremia, pulmonary hypertension, severe hemorrhagic diathesis, and cervical C1/C2 arthritis.
2. The subject has had lung surgery which may interfere with bronchoscopy.
3. Known history of allergic/hypersensitivity reactions to medications used during and for perioperative care associated with the bronchoscopy/BAL procedures, such as local anesthetics, sedatives, pain control medications.

4. The subject is receiving or requires long-term (>4 weeks) immunosuppressive therapy, such as systemic corticosteroids at doses greater than 10 mg/day of prednisone (or its equivalent), mycophenolate mofetil, azathioprine, cyclophosphamide, and rituximab.
5. If a subject is receiving anticoagulant or anti-platelet therapy (such as warfarin and clopidogrel), the subject is unwilling to or unable to safely discontinue anticoagulant or anti-platelet therapy within 7 days prior to until at least 24 hours after the BAL procedures. An exception is low-dose aspirin alone which is allowed.

9.5 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) 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 withdraw or discontinuation) are described in Section 10.6, Section 20.2, and Section 20.3.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). 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 also will be 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 completion 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 develops a serious AE, which, based on the medical judgment of the investigator, prevents completion of participation in the study.
4. The subject fails to comply with protocol requirements or procedures that may include, but are not limited to:
 - The subject frequently misses scheduled administration of the IP, defined as missing a total of >20% (ie, >5) of planned infusions, or 4 or more consecutive weekly infusions.

- The subject is treated with any A1PI product (including commercially available GLASSIA) other than IP.
 - The subject participates in another clinical study and/or receives an investigational product/device other than IP.
5. The sponsor terminates the study.

For subjects undergoing BAL procedures, if no evaluable BAL samples can be obtained from any of the 3 lobes attempted during the baseline BAL visit, the subject will not be randomized and will be discontinued from the study. If acceptable BAL samples can be obtained during the baseline BAL visit but not from any of the 3 lobes attempted during the on-treatment BAL visit (between Week 12 to Week 14), the subject will continue to complete the remaining infusion visits and the study completion visit. These subjects would not be considered as a BAL evaluable subject. Acceptability criteria of BAL samples and definition of evaluable subjects are provided in Section 20.5 and Figure 20-2.

10. STUDY PROCEDURES

The overall study flow chart is illustrated in Figure 20-1 (Supplement 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 Schedule of Clinical Laboratory Assessments.

10.1 Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form [ICF]) is considered enrolled in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the subject identification code (SIC): protocol identifier (eg, 471101) 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 ICF). For example, the third subject who signed an ICF at study site 02 will be identified as Subject 471101-020003. 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 personal 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

10.3.1 Screening Visit

After informed consent has been obtained from the subject and/or their legally authorized representative, subjects will be screened on-site for eligibility based on the Inclusion and Exclusion Criteria defined in Section 9.1 and Section 9.2, respectively. Additionally, for subjects who are to undergo BAL assessments in the study, randomization is to take place after the subject has met all eligibility criteria (including those listed in Section 9.3 and Section 9.4) and successfully undergone the baseline BAL visit with evaluable BAL samples collected.

The study site is responsible for maintaining an enrollment/screening log that includes all subjects enrolled. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome.

10.3.1.1 Confirmation of Severe Congenital A1PI Deficiency

To establish eligibility for participation in the study, the subject's diagnosis of severe congenital A1PI deficiency must be confirmed during screening that includes 2 tests:

- A1PI genotype
- Measurement of endogenous circulating A1PI level

Subjects must have A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, or Pi*Null/Null, AND circulating antigenic A1PI level of <8 µM in order to meet eligibility criteria. A subject's past (pre-study) records, if available, may be used as an initial assessment (eg, a subject will be considered ineligible based on past record of Pi*SZ genotype). However, for confirmation of congenital A1PI deficiency, all otherwise potentially eligible subjects will be required to undergo A1PI genotype and circulating A1PI tests during screening. Results of these screening tests will be used to establish the subject's eligibility for participation in the study.

For those subjects who are receiving or have recently been exposed to A1PI augmentation therapy at the time of study enrollment, the presence of exogenously administered A1PI may interfere with the verification of endogenous circulating A1PI levels. Therefore, these subjects will be required to have their pre-study A1PI therapy withdrawn for a minimum of 4 weeks to allow A1PI to return to the subject's unaugmented levels. The 4-week washout period should be adequate, based on an average A1PI half-life of 4.6 daysⁱ and that typically 4 to 5 half-lives would be required

(ie, 18 to 23 days). However, in light of inter-subject variability in A1PI half-life, some subjects may require a longer washout period. Therefore, screening A1PI measurement may be repeated in the event of suspected inadequate washout resulting in initial screening A1PI level of $>8 \mu\text{M}$.

During the washout period, these subjects will be allowed to undergo other screening procedures (Supplement 20.2 and Supplement 20.3).

10.3.1.2 Pulmonary Function Tests

10.3.1.2.1 Spirometry

Spirometry tests are to be conducted according to standard guidelines published by the American Thoracic Society and European Respiratory Society.^{26; 27} Whenever possible, all measurements should be performed with the same equipment around the same time of the day (± 2 hours) during site visits to minimize equipment and diurnal variability. All spirometric measurements (FEV₁ 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 salbutamol [2 x 200 μg or 4 x 100 μg] or its equivalent). Spirometric measurements (FEV₁ 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.

10.3.1.2.2 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. In order to minimize test variability, all determinations will be conducted in accordance with recommendations for the standardization of testing published by the American Thoracic Society (ATS) and European Respiratory Society (ERS)^{28; 29} and general guidelines for lung function testing.²⁰ Gas volumes are reported with body temperature and pressure saturated corrections and results are expressed in absolute values and as percentage of predicted values.

10.3.1.3 Rescreening

Subjects may be rescreened once for study eligibility. Subjects who have failed screening for any of the following reasons may be rescreened:

1. Circulating antigenic A1PI level of ≥ 8 μM that is suspected to be due to inadequate washout of the prior A1PI therapy
2. Erroneous screening results
3. Pulmonary exacerbation at the time of initial screening (Note: subjects may be re-screened 4 weeks after the clinical resolution of an exacerbation)
4. Ineligibility due to failure to meet protocol pre-specified time intervals (eg, inclusion criteria #7 and 8, and exclusion criteria #7 and 15)

If a subject is to be re-screened, the study completion/termination CRF should be completed. The subject or his/her legally authorized representative must sign a new ICF prior to rescreening procedures. A new SIC will be assigned, and new CRFs will be used for the subject upon re-enrollment. All screening procedures, with the exception of A1PI genotype (unless repeat is necessary, eg, the test was not performed or erroneous result was obtained during initial screening), will be performed during rescreening.

10.3.2 Infusion Visits

GLASSIA will be administered as IV infusions at 60 mg/kg BW every week (± 2 days) for a total of 25 infusions. Scheduling of all infusion or study visits will be based on the date of the first IP infusion visit (Week 1, Day 1).

10.3.2.1 IP Administration

Description of GLASSIA treatment including treatment period, dose and dosing frequency, mode of administration, as well as preparation of infusion solution are detailed provided in Section 8.7.

The first infusion (Week 1), as well as infusions during Week 13 and Week 25, must be administered at the study site to facilitate monitoring and reporting of potential AEs associated with GLASSIA infusions. At the investigator's discretion, all other infusions may be administered at the study site or at another suitable location (eg, the subject's home) by a qualified healthcare professional, as acceptable per local regulations and standard practices of the study site.

During Weeks 1, 7, 13, 19, and 25 infusion visits, vital signs (ie, body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure; see Section 12.10 and Table 20.3-1 for additional details) are to be taken on the day of infusion at any time

prior to the start of an infusion, at each rate reduction due to AE(s) and/or infusion interruption/discontinuation due to AE(s), and within 90 minutes after the completion of an infusion. The investigator should be contacted to determine appropriate action to be taken, as necessary, if vital signs meet any of the following criteria:

- Systolic blood pressure ≤ 80 mm Hg or ≥ 180 mm Hg and/or diastolic blood pressure: ≤ 50 mm Hg or ≥ 110 mm Hg
- Pulse rate ≤ 48 beats/min or ≥ 110 beats/min
- Respiratory rate ≤ 8 breaths/min or ≥ 24 breaths/min
- Body temperature ≥ 38.2 °C (101 °F)

For each infusion, the following IP administration information will be recorded in the appropriate CRF(s):

- Date, start and end time of the infusion
- Planned infusion volume
- Actual volume infused
- Infusion rate, including each infusion rate change (if any) and reason
- Infusion interruptions or early discontinuation (if any), including the time of infusion interruption (or early stop) and restart
- AE(s)
- Concomitant use of any medications and any non-drug therapies, including those used to treat AE(s)

10.3.2.2 Management of Treatment-Emergent (S)AEs

Mild-to-moderate non-serious AEs or other constitutional symptoms that developed during an infusion may be treated by standard-of-care medical interventions appropriate for the AE at the investigator's discretion. In the event that the AE continues or increase in severity despite interventions, the infusion rate may be decreased by 0.04 mL/kg BW/min or the infusion may be temporarily interrupted at the investigator's discretion. If the AE is not resolving, the infusion rate may be further decreased in a stepwise manner by 0.04 mL/kg BW/min or discontinued. Once an AE resolves, the infusion may be resumed or continued at an infusion rate as tolerated by the subject (but not to exceed 0.2 mL/kg BW/min) at the discretion of the investigator.

If a severe, non-serious AE or SAE occurs during an infusion, the infusion should be interrupted pending assessment by the investigator, and appropriate action is to be taken to treat the AE. The infusion may be restarted if the AE resolves in response to interventions and/or reduction in infusion rate and if it's deemed safe by the investigator.

In the event of a life-threatening SAE, study personnel should take immediate steps to preserve the subject's well-being and call for emergency assistance, as well as contact the investigator. All SAEs must be reported on the SAER form and transmitted to the sponsor within 24 hours after becoming aware of the event.

For moderate-to-severe hypersensitivity reactions (ie, urticaria, low blood pressure, angioedema, or wheezing), the infusion should be stopped immediately and the subject should be treated according to the standard of care at the discretion of the investigator. Prior to further IP administrations, the investigator should consult the sponsor's Medical Monitor.

In the event a subject develops a rash at any time during the study, the nature, severity, extent of the eruption, its temporal relationship to the last IP administration, and the likely cause(s) should be examined prior to the next scheduled infusion. Management of rashes includes, but is not limited to, the following:

- Minor rashes are those involving 10% of body surface or less without bleeding or signs of secondary infection. Minor rashes may be treated as indicated with topical medications, including anti-pruritic and corticosteroid creams. Infusions can be continued if the rash is confirmed to be minor and/or deemed unrelated to IP.

- Major rashes are those that involve more than 10% of the body surface, are progressive, are associated with hemorrhage and/or secondary infection, or require systemic corticosteroid treatment. These should be treated appropriately and infusions should be discontinued immediately until the condition has resolved completely or is judged to be not clinically significant. Procedures (eg, biopsy of the lesion) may be performed to investigate the pathophysiology of the rash. At the discretion of the investigator, IP treatment may be resumed only after the rash has resolved and the subject's condition is deemed medically safe and appropriate. Pre-medications such as oral or topical corticosteroid treatment may be administered for the subsequent 2 infusions, as applicable, at the discretion of the investigator in accordance with the standard of care at the investigative site. Subjects with recurrent major rashes, rashes that recur upon re-challenge of IP despite (pre-)medication(s), or rashes that do not resolve within 6 weeks will be discontinued from further IP administration and will be followed as outlined in Section 9.5.

Any rate reductions, interruptions or discontinuation of an infusion and, if applicable, any medications and/or non-drug therapies used to treat AE(s), must be recorded in the appropriate CRF(s).

10.3.2.3 Pre-Medications

If the same type of mild-to-moderate, non-serious AE expected to be related to IP infusion (eg, headache, chills, fever, flushing, and malaise) or other constitutional symptoms recurs for 2 or more infusions, the subject may be pre-medicated for subsequent infusion(s) at the discretion of the investigator in accordance with the standard of care at the investigative site. The use of any pre-medications must be recorded in the appropriate CRF(s).

10.3.2.4 Post-Infusion Follow-Up

Following each infusion visit, the investigator/designee will contact the subject to document AEs and concomitant medications, as well as non-drug therapies, which may have occurred within 24 and 72 hours after the completion of an infusion visit. Follow-up should be conducted within 1 business day after 72 hours following the completion of the infusion.

10.3.3 Clinical Assessment Visits

During the treatment period, subjects will be asked to return to the study site during Week 13 and Week 25 for clinical and safety laboratory assessments, as well as plasma

A1PI measurements. Additional blood samples will be drawn for the monitoring of plasma A1PI levels during Week 7 and Week 19, which may take place at study site or at another suitable location (eg, the subject's home) by a qualified healthcare professional. Following the last infusion (Week 25), subjects will return to the study site 7 ± 3 days post-infusion for study completion assessments.

A detailed list of assessments to be performed at each clinical assessment visit is provided in Supplement 20.2 and Supplement 20.3.

10.3.4 BAL Visits

This section applies to subjects who are to undergo BAL procedures. Bronchoscopy/BAL procedure will be waived for subjects who are enrolled after at least 15 BAL evaluable subjects have been obtained.

Subjects who have met all eligibility criteria (including the additional eligibility criteria for undergoing the BAL procedure outlined in Section 9.3 and Section 9.4) will undergo bronchoscopy/BAL procedure on 2 occasions: at baseline (prior to randomization) and following initiation of GLASSIA treatment for 12 to 14 weeks.

For subjects who have received A1PI augmentation therapy prior to study entry, plasma samples for baseline antigenic A1PI levels will be collected within 10 days prior to the baseline BAL visit to verify the adequacy of the washout from A1PI therapy prior to performing BAL.

In order for a subject to be randomized and remain in the study, the subject must have at least one lobe with an acceptable BAL sample collected at the baseline BAL visit. Following the baseline BAL procedure, subjects will be allowed to recover for a minimum of 2 days prior to the first IP infusion. If no acceptable BAL samples can be obtained from any of the 3 lobes attempted during the baseline BAL visit, the subject will undergo early termination visit and be discontinued from the study.

During GLASSIA augmentation therapy, the subject will be asked to undergo the on-treatment BAL visit between Week 12 and Week 14. The on-treatment bronchoscopy/BAL procedure will be conducted at least 3 days after the last IP infusion but with a minimum of 2 days prior to the next IP infusion to allow subjects to recover from the BAL procedure. Subjects with acceptable BAL samples obtained from at least one lobe will be considered as evaluable subject. If acceptable BAL samples cannot be obtained from any of the 3 lobes attempted during the on-treatment BAL visit, the subject will continue to complete the remaining infusion visits through Week 25 and the study

completion visit (Week 26). These subjects, however, would not be considered as a BAL evaluable subject. See Section 20.5 and Figure 20-2 for more detailed BAL sample acceptability criteria and definition of evaluable subjects. New subjects may be enrolled to achieve the target of 15 to 18 evaluable subjects.

During the BAL visits, plasma samples will be collected within 2 hours prior to the BAL procedure for the measurement of plasma urea, as well as plasma antigenic and functional A1PI levels. Vital signs will be measured within 2 hours prior to each BAL procedure and within 1 hour after the completion of the BAL procedure. Pre-BAL vital signs are to be assessed prior to bronchodilator and local anesthesia administration. The subject should be monitored for ECG, blood pressure, respiratory rate, and pulse oximetry during the procedure in accordance with standard practice at the local institution. The subject will remain in the hospital/clinic until, in the investigator's medical judgment, it is safe to discharge the subject. Subjects will be followed for post-BAL safety monitoring (ie, AEs and concomitant medications/non-drug therapies) at the study site or by telephone within 2 weeks after each BAL procedure.

In order to assess the effects of GLASSIA maintenance treatment on the ELF A1PI levels, it is important for the on-treatment BAL procedure be performed after stable dosing of GLASSIA has been maintained for at least 4 half-lives of A1PI (ie, average half-life ~4.6 days, see GLASSIA package insert). Thus, should a subject miss 1 or more consecutive GLASSIA infusion(s) within 4 week(s) immediately prior to the scheduled on-treatment BAL visit, the BAL procedure will be rescheduled to occur after the subject has received at least 4 consecutive weekly GLASSIA administrations. The rescheduled BAL procedure will be performed at least 3 days after the last IP infusion and at least 2 days prior to the next IP infusion.

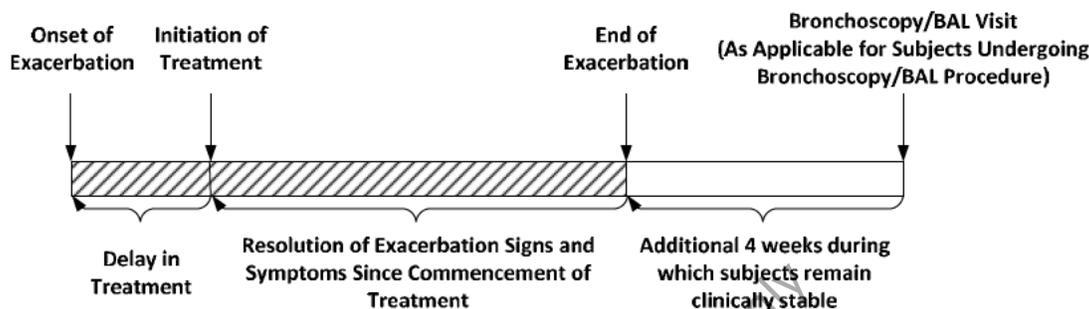
Detailed bronchoscopy/BAL procedures are provided in Supplement 20.5.

10.4 COPD Exacerbation and Lower Respiratory Tract Infection (LRTI)

An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and lead to a change in medication. The onset of an exacerbation is defined as the first day of an increase in or new onset of more than one of the respiratory symptoms (cough, sputum, sputum purulence, wheezing, or dyspnea), compared to the subject's usual clinical state, for at least 2 consecutive days and requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) corticosteroids. The end of an exacerbation is defined as the first day that any signs and symptoms of COPD exacerbation and/or LRTI symptoms are no longer clinically evident (ie, the first day that a subject returns to his/her

usual clinical state) for at least 2 consecutive days. As depicted in Figure 10-1, the total length of the episode includes any delay in treatment (time taken for treatment to be initiated after the onset of exacerbation) and time to resolution of signs and symptoms.^{30,31}

Figure 10-1
Exacerbation of COPD



If a subject experiences a moderate or severe COPD exacerbation and/or LRTI during the screening period, baseline BAL visit will be postponed once in order for the subject to recover from the exacerbation (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically evident) and remain stable for at least 4 weeks after the end of exacerbation. If a moderate or severe episode of COPD exacerbation and/or LRTI occurs during the treatment phase, the subject should continue with the planned study visits and to receive weekly infusions of GLASSIA as planned, unless deemed medically inappropriate by the investigator. However, the on-treatment BAL visit will be postponed until clinical resolution of the exacerbation (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically evident) plus an additional minimum period of 4 weeks after the end of exacerbation.

The severity of an COPD exacerbation and/or LRTI will be categorized as mild, moderate, or severe 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 admission to hospital)
- Severe – hospitalization (an emergency department stay >24 hours is considered a hospitalization)

Any occurrences of COPD exacerbation and/or LRTI are to be recorded on the AE CRF.

10.5 Medications and Non-Drug Therapies

The following medications are **not** permitted at any time during the course of the study:

- Any A1PI augmentation therapy other than IP in this study; commercially available GLASSIA is also not permitted
- Any investigational drug, biologic, or device other than IP in this study

A subject who has taken any of the above medications will be discontinued from further treatment and/or from the study.

The following medications are not permitted within a pre-specified time interval prior to each BAL procedure:

- Immunosuppressive therapies (such as systemic corticosteroids at doses greater than 10 mg/day of prednisone or its equivalent, mycophenolate mofetil, azathioprine, and cyclophosphamide) within 4 weeks prior to and during the BAL procedures
 - Rituximab at any time during the study
- Anticoagulant or anti-platelet therapy (such as warfarin and clopidogrel) within 7 days prior to and during the BAL procedures, with the exception of low-dose aspirin which is allowed

The following medications are permitted during the course of the study provided that the dosage remains stable throughout the course of the study:

1. Any respiratory medications including inhaled bronchodilators, inhaled anticholinergics, inhaled corticosteroids, or low-dose systemic corticosteroids (prednisone \leq 10 mg/day or its equivalent)
2. Theophylline
3. Other medications that a subject is taking for a pre-existing medical condition except for those listed under prohibited medications above

Dosages of permitted concomitant medications are to remain stable throughout the course of the study, unless otherwise medically indicated.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). 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. Subjects who are discontinued early from the study prior to receiving any IP administration will not need to undergo early termination procedures, except for those subjects who have undergone the baseline BAL procedure in which case subjects will be followed for potential post-BAL complications for a period of time in accordance with local institutional standard practice but not to exceed 30 days.

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 Schedule of Clinical Laboratory Assessments.

In the event of subject discontinuation due to an (S)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.

10.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a qualified healthcare professional at the study site or at another suitable location (eg, the subject's home or infusion center), and thus, no separate procedures will be used to monitor subject compliance.

Trough antigenic and functional A1-PI levels in plasma would be determined as a check on subject's compliance/adherence to treatment.

11. ASSESSMENT OF EFFICACY

11.1 ELF Antigenic and Functional A1PI Levels

This study will evaluate the effects of GLASSIA weekly augmentation therapy on the A1PI levels in the ELF.

BAL samples will be analyzed for the determination of the following in the BAL fluid using validated bioanalytical assays at a qualified laboratory:

1. Antigenic A1PI level
2. Functional A1PI (ANEC) level
3. Urea level

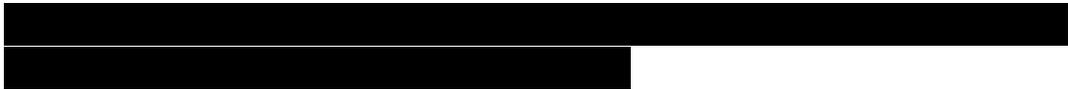
ELF antigenic and functional A1PI levels will be estimated based on the respective values measured in the BAL fluid using the plasma-to-BAL urea correction method. This approach is based on the fact that urea is freely diffusible through most body compartments, including the alveolar wall. A dilution factor, k, will be determined with the following formula: dilution factor $k = U_p$ (concentration of urea in plasma)/ U_{BAL} (concentration of urea in BAL fluid). Using this dilution factor, quantitative measurements of ELF A1PI and [REDACTED] will be corrected accordingly.

Detailed information for the BAL visits and bronchoscopy/BAL procedures can be found in Section 10.3.4 and Supplement 20.5.

11.2 [REDACTED]

[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 the 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 human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

Uncomplicated pregnancies, following maternal or paternal exposure to the 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 Plus Suspected Adverse Reactions

An AR plus suspected AR 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 ARs 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, GLASSIA package insert). “Unexpected” also refers to the AEs that are mentioned in the Reference Safety Information 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.

Any AEs (expected and unexpected) will be recorded on the AE CRF.

12.1.1.5 Adverse Events Potentially Associated with Protein Aggregates

The safety database will be reviewed and assessed for AEs that may potentially be associated with protein aggregates in GLASSIA solution.

12.1.1.6 Preexisting Diseases

Preexisting diseases that are present before entry into 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 occurrences of COPD exacerbation and/or LRTI are to be recorded on the AE CRF (see Section 10.4).

12.1.2 Assessment of Adverse Events

Each AE from the first IP exposure until study completion/early discontinuation from the study 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/termination visit, whichever comes first. AE and other CRF(s), as applicable, will be updated if additional follow-up information is collected/reported prior to study completion (no additional reporting on CRF(s) is necessary after study completion).

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 Form and followed-up at 1 year post-delivery, if feasible.

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.

For the purposes of this study, each AE (expected and unexpected) experienced by a subject undergoing bronchoscopy/BAL procedure will be recorded on the AE CRF.

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 physiological 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 following completion of each 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 is notified of the urgent measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

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 non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) (eg, washout of a

subject's pre-study A1PI augmentation therapy, bronchoscopy/BAL procedures) will be recorded on the AE CRF. These events, if occurred before the first IP exposure, will not be considered as AEs and will not be included in the analysis of AEs. On the other hand, these events, if occurred after initiation of IP treatment, will be considered as AEs and will be 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 (as 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.

All medications taken and non-drug therapies received from enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in Table 20.2-1), 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 12.1.1.6), 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.

12.7 Clinical Laboratory Parameters

The schedule of sample collection for clinical laboratory assessments is provided in Table 20.3-1 Clinical Laboratory Assessments. Detailed requirements for sample collection and handling can be found in the Laboratory Manual.

12.7.1 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, and neutrophils), absolute neutrophil count (ANC), absolute lymphocyte count, reticulocyte count, and platelet count.

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

Blood will be collected for the assessment of hematology and clinical chemistry parameters during each of the following visits: screening, Week 1 (prior to the first IP infusion; this will serve as baseline value), Week 13, Week 25, and at study completion (Week 26) visit. Samples to be collected on the day of IP administration (ie, Week 1, Week 13, and Week 25) must be collected prior to the start of IP infusion. Subjects who are discontinued early from the study will be asked to undergo hematology and clinical chemistry assessments at the Early Termination visit, only if these subjects have been exposed to IP.

Hematology and clinical chemistry assessments will be performed on ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood and serum samples, respectively, at a central laboratory.

12.7.2 Complement Activation and Immune Complex Panel

Complement activation and immune complex panel will consist of serum complement component 3 (C3), complement component 4 (C4), total complement (50% hemolytic complement activity of serum; CH50), C1q binding, and circulating immune complexes.

Blood will be collected to obtain serum samples for the assessment of complement activation and circulating immune complexes during each of the following visits: Week 1 (prior to the first IP infusion; this will serve as baseline value), Week 13, Week 25, and at study completion (Week 26) visit. Samples to be collected on the day of IP administration (ie, Week 1, Week 13, and Week 25) must be collected prior to the start of IP infusion. Subjects who are discontinued early from the study will be asked to undergo complement activation and immune complex evaluation at the Early Termination visit, only if these subjects have been exposed to IP.

Complement activation and immune complex assessments will be performed at a central laboratory.

12.7.3 Viral Serology and Nucleic Acid Tests

Viral serology tests for HAV antibody, hepatitis B virus surface antigen (HBsAg), HCV antibody, and HIV-1/HIV-2 antibody will be performed at screening for subject eligibility determination.

Viral testing for B19V will consist of B19V antibody serology test and NAT, based on real-time polymerase chain reaction (PCR) detection of B19V DNA. Serum samples will be collected prior to the first IP infusion during Week 1 (which serves as the baseline value) and at the last infusion visit (Week 25). If a subject's Week 1 pre-dose sample is tested positive, then no further testing (eg, Week 25) is required. Any evidence of seroconversion (eg, change from a negative test result at baseline [Week 1 prior to the first IP infusion] to a positive result at a post-baseline assessment) for B19V should be re-tested. Subjects who are discontinued early from the study will be asked to undergo viral serology and NAT testing at the Early Termination visit, only if these subjects have been exposed to IP.

Serology testing and NAT will be performed at a central laboratory.

12.7.4 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). Urinalysis will be performed during each of the following visits:

screening, Week 1 (prior to the first IP infusion; this will serve as baseline value), Week 13, Week 25, and at study completion (Week 26) visit. Samples to be collected on the day of IP administration (ie, Week 1, Week 13, and Week 25) must be collected prior to the start of IP infusion. Urinalysis will be performed at a central laboratory.

Pregnancy test will be performed for females of childbearing potential at screening and at study completion (Week 26) visit. 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.

12.7.5 Assessment of Clinical Laboratory Values

12.7.5.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each safety-related laboratory value will be recorded on the 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 a 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 12.1.1.6), 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 seroconversion result for B19V should be re-tested. Any abnormal value that persists should be followed at the discretion of the investigator.

In addition to investigator's assessment of the clinical significance of laboratory abnormalities, clinical laboratory abnormalities with values that meet the criteria listed in Section 20.4 will be separately analyzed and reported.

12.7.6 Biobanking

Backup samples should be taken and stored appropriately for additional analysis, if necessary. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test 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)
 - Plasma urea
- 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 assays
 - Anti-A1PI antibodies for neutralizing antibody assay
- BAL 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):
 - BAL antigenic A1PI
 - BAL functional A1PI (ie, ANEC)
 - BAL urea

Backup samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test or an AE. 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, and then the samples will subsequently be destroyed.

12.8 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 μ M 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 prior to the start of IP infusion) during Week 7, Week 13, Week 19, and Week 25, and at the study completion (Week 26) visit.

For subjects who are to undergo BAL assessments, plasma samples for baseline antigenic A1PI level will be collected within 10 days prior to the baseline BAL visit to verify the adequacy of the washout from A1PI therapy prior to performing the baseline BAL visit. Then, on the day of the baseline BAL visit, plasma samples for the measurement of antigenic and functional A1PI levels will be collected simultaneously with plasma samples for urea measurements within 2 hours prior to the BAL procedure. These values will be used for the calculation of the corresponding A1PI levels in ELF using plasma-to-BAL urea correction method. Sample collection for plasma antigenic and functional A1PI and urea will be repeated on the day of the on-treatment BAL visit within 2 hours prior to the BAL procedure (see Section 10.3.4).

Subjects who are discontinued early from the study after having been exposed to IP administration 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 analysis for the determination of plasma antigenic and functional A1PI levels will be performed using validated bioanalytical assays at a qualified laboratory.

12.9 Immunogenicity

Blood will be collected to obtain serum samples for monitoring the appearance/presence of anti-A1PI antibodies 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 Week 13 and Week 25, and at study completion (Week 26) visit. 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 immunogenicity assessment at the Early Termination visit.

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.

Each sample is to be stored as duplicate aliquots each with sufficient volume needed for sample analysis. Detailed sample handling and storage instructions will be provided in the laboratory manual.

Anti-A1PI antibodies will be detected using validated binding and neutralizing anti-A1PI antibody assays at a qualified immunoassay laboratory. The presence of anti-A1PI

antibodies in a sample will be detected using a screening assay and confirmed using a confirmatory assay. Only those samples with confirmed positive results will be further analyzed for the examination for the presence of neutralizing antibodies.

12.10 Vital Signs

Body height (in or cm) will be collected at screening only. Body weight (lb or kg) will be measured at screening and at study visits during Weeks 1, 7, 13, 19, and 25.

Vital signs will include body temperature ($^{\circ}\text{C}$ or $^{\circ}\text{F}$), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Blood pressure measurements will be taken when subjects are in either the sitting or supine position; the same position should preferably be maintained each time a blood pressure is measured. These vital signs will be measured at screening, during treatment period (Weeks 1, 7, 13, 19, and 25), and at study completion (Week 26)/early termination visit (see also Section 10.3.2.1 and Table 20.3-1).

For each of the IP infusion visits where vital signs are to be taken, vital signs will be recorded at any time prior to the start of an infusion, at each rate reduction due to AE(s) and/or infusion interruption/discontinuation due to AE(s), and within 90 minutes after the completion of an infusion. The investigator should be contacted to determine appropriate action to be taken, as necessary, if vital signs meet any of the following criteria:

- Systolic blood pressure ≤ 80 mm Hg or ≥ 180 mm Hg and/or diastolic blood pressure: ≤ 50 mm Hg or ≥ 110 mm Hg
- Pulse rate ≤ 48 beats/min or ≥ 110 beats/min
- Respiratory rate ≤ 8 breaths/min or ≥ 24 breaths/min
- Body temperature ≥ 38.2 $^{\circ}\text{C}$ (101 $^{\circ}\text{F}$)

For subjects undergoing BAL procedures, vital signs will be measured within 2 hours prior to each BAL procedure and within 1 hour after the completion of the BAL procedure. Pre-BAL vital signs are to be performed prior to the administration of bronchodilator and local anesthesia.

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 vital sign 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.

13. STATISTICS

13.1 Sample Size and Power Calculations

The sample size calculation for the BAL component of the study was based on the natural log transformed primary endpoint data, ELF antigenic A1PI level (nM), generated during Baxter's Clinical Study 460502. In Clinical Study 460502, a mean difference from pre- to post-treatment in ELF antigenic A1PI of 1.32 with standard deviation of 0.96 on natural log scale was observed. Using this variance estimate, a sample size of 15 evaluable subjects should be sufficient to detect a mean difference in the natural log transformed ELF antigenic A1PI of approximately 0.87 with 90% power, using a paired t-test and a one-sided significance level of 0.025.

A sample size of 15 evaluable subjects will also be sufficient to detect a mean difference in the natural log transformed ELF functional A1PI (ANEC) of approximately 1.04, with 90% power, assuming a standard deviation in the differences between pre- and post-treatment ANEC values to be 20% higher than that for antigenic A1PI.

Based on the experience from Clinical Study 460502, it is estimated that approximately 26 to 32 subjects will be needed in order to achieve 15 to 18 BAL evaluable subjects, respectively. Thus, an overall study enrollment target of 36 subjects should be adequate to meet the target sample size for the BAL component of the study.

13.2 Datasets and Analysis Cohorts

13.2.1 Full Analysis Set

The full analysis set (FAS) will include all subjects who received at least one IP infusion and have at least one available A1PI measurement during the treatment period.

13.2.2 Per-Protocol Analysis Set

The per-protocol (PP) analysis set will include a subset of the full analysis set, comprising subjects with no major protocol deviations. For the purpose of statistical analysis, major deviations include, but are not limited to, the following: failure to comply with the washout period for pre-study A1PI augmentation therapy, missing two or more consecutive weekly infusions and/or >15% of planned infusions, and use of an A1PI product (including commercially available GLASSIA) other than IP during the study treatment period.

13.2.3 BAL Analysis Set

The BAL analysis set will include a subset of the FAS analysis set, comprising subjects who meet all of the following criteria:

- Subjects who have met all study inclusion and exclusion criteria, including additional BAL-related eligibility criteria
- Subjects have successfully completed both the baseline and the on-treatment BAL visits and have a minimum of one evaluable sample per BAL visit with no missing infusion(s) within 4 weeks immediately preceding the on-treatment BAL procedure
- Subjects must have available ELF data for both the baseline and the on-treatment BAL visits in order to be included in the efficacy analyses for the assessment of ELF analyte levels following GLASSIA augmentation therapy.

13.2.4 Safety Analysis Set

The safety analysis set will include all subjects enrolled in the study who received at least one IP infusion.

13.3 Handling of Missing, Unused, and Spurious Data

No missing data imputation will be performed.

13.4 Methods of Analysis

13.4.1 Efficacy Outcome Measures

Antigenic and functional A1PI levels in the ELF will be estimated based on the corresponding BAL measurements at each time point using plasma-to-BAL urea correction method. ELF antigenic and functional A1PI levels, as well as changes from baseline, will be summarized descriptively and displayed graphically (data permitting) based on data pooled across both treatment arms. For a given subject, if BAL measurements are obtained from more than 1 lung lobe, then the urea-corrected values will be averaged at the corresponding time point prior to being summarized.

Since an increase from baseline in the mean ELF levels of antigenic A1PI is expected, a one-sided paired t-test will be conducted at an α -level of 0.025 with the following null and alternative hypotheses where the mean change in antigenic A1PI from baseline to the on-treatment BAL measurement is μ_d :

Ho: Mean change in antigenic A1PI in the ELF from baseline to the on-treatment measurement will be less than or equal to zero.

$$H_0: \mu_d \leq 0$$

H1: Mean change in antigenic A1PI in the ELF from baseline to the on-treatment measurement will be greater than zero.

$$H_1: \mu_d > 0$$

The mean change in functional A1PI (ANEC) from baseline to on-treatment measurement will be analyzed in a similar fashion, if data permit. The natural logarithm transformation may be applied to the ELF antigenic or functional A1PI values prior to analysis if the distributions are highly skewed. This analysis will be conducted with the BAL analysis set.

[REDACTED]

Changes from baseline in ELF and plasma antigenic and functional A1PI levels, as well as [REDACTED], will be summarized in the following subgroups: by sex, age (≤ 65 , >65), race, and ethnicity. [REDACTED]

13.4.2 Exposure

Plasma trough antigenic and functional A1PI levels, as well as changes from baseline, will be summarized descriptively and displayed graphically (data permitting) based on data pooled across both treatment arms. Plasma antigenic and functional A1PI levels obtained at the baseline and on-treatment BAL visits will be summarized separately and, data permitting, to be correlated with the corresponding values in the ELF. Plasma A1PI levels obtained at the study completion (Week 26) or early termination visit will not be part of this analysis. These analyses will be conducted with both the FAS and the PP analysis sets.

In the event of anti-A1PI antibody formation is detected, the individual antigenic and functional A1PI levels may be evaluated in conjunction with binding and neutralizing anti-A1PI antibody titers, as applicable.

13.4.3 Safety Outcome Measures

The safety analysis set will be used for the following analyses, unless otherwise stated:

AEs that are considered potentially related to the presence of protein aggregates or immune-mediated will be summarized descriptively with 95% confidence intervals (CIs) as appropriate for each AE of interest by each treatment arm and, if appropriate, pooled across both treatment arms. In the event of any clinically significant trends in treatment-emergent AE(s) of interest, further analysis including potential correlation with the presence of particulates in the GLASSIA solution will be performed.

ARs plus suspected ARs, using a time frame for AE onset of (a) during and within 24 hours and (b) during and within 72 hours of completion of an infusion, will be tabulated separately and presented according to seriousness, severity, and causality, as well as by MedDRA preferred term. Similar tabulation of data will be conducted for AEs and SAEs.

The number (proportion) of subjects experiencing SAEs, AEs, related AEs, and/or ARs plus suspected ARs will be summarized by each treatment arm and, if appropriate, pooled across both treatment arms with their point estimates and exact 95% CIs.

The number (proportion) of infusions (defined as percentage of the total number of infusions administered) temporally associated with AEs or SAEs (defined as during or within (a) 24 hours and (b) 72 hours of completion of infusion) will be computed for each subject. The median (95% CI), minimum, and maximum of these numbers (or percentages, respectively) will be tabulated.

The number (proportion) of infusions (defined as percentage of the total number of infusions administered) causally associated with AEs or SAEs will be computed for each subject. The median (95% CI), minimum, and maximum of these numbers (or percentages, respectively) will be tabulated.

The number (proportion) of infusions (defined as percentage of the total number of infusions administered) associated with ARs will be computed for each subject. The median (95% CI), minimum, and maximum of these numbers (or percentages, respectively) will be tabulated.

The number (proportion) of infusions that are discontinued, slowed, or interrupted due to an AE will be summarized. The rates of AEs and ARs expressed as the number of events that occurred in total number of infusions administered will be provided by MedDRA term.

The proportion of subjects who develop binding and/or neutralizing anti-A1PI antibodies will be summarized with their point estimates and exact 95% CIs. Treatment-emergent anti-A1PI antibody data will be listed along with the corresponding plasma antigenic and functional A1PI levels in the individual subject. Additionally, temporal relationship of anti-A1PI antibody formation with potentially immune-related AEs, if any, will be examined.

The number (proportion) of subjects who experienced a shift from normal or clinically non-significant abnormal laboratory values at baseline to clinically significant abnormal laboratory values will be summarized with their point estimates and exact 95% CIs. Any clinically significant laboratory values that are considered as clinically significant by the investigator (ie, reported as AEs), as well as in accordance with the thresholds provided in Section 20.4, will be analyzed and reported, including shift tables.

Changes in vital signs obtained pre- and post-infusions, as well as pre- and post-BAL procedures as applicable, will be provided in a listing.

The proportion of subjects with confirmed treatment-emergent seroconversion by viral serology or nucleic acid test for B19V during or following treatment with GLASSIA will be summarized with exact 95% CIs.

Safety parameters will be summarized descriptively by sex, age (≤ 65 , >65), race, and ethnicity. No hypothesis tests are planned; however, [REDACTED]

AEs that occur before treatment will be listed separately.

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.

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.

15.4 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 auditing 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 (Baxter) 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; each type of assay is planned to be conducted at a single laboratory facility for consistency and standardization.

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, ICF, 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 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 ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(ies), where applicable, (see Section 16.2). The ICF 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 ICF, 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 ICF that have 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

A Data Monitoring Committee (DMC) will not be used for this study, since the IP is already a licensed product and the dosing regimen being evaluated is already approved for chronic treatment in the patient population to be enrolled in this study.

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 Documents 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 ICFs, 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 in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is 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

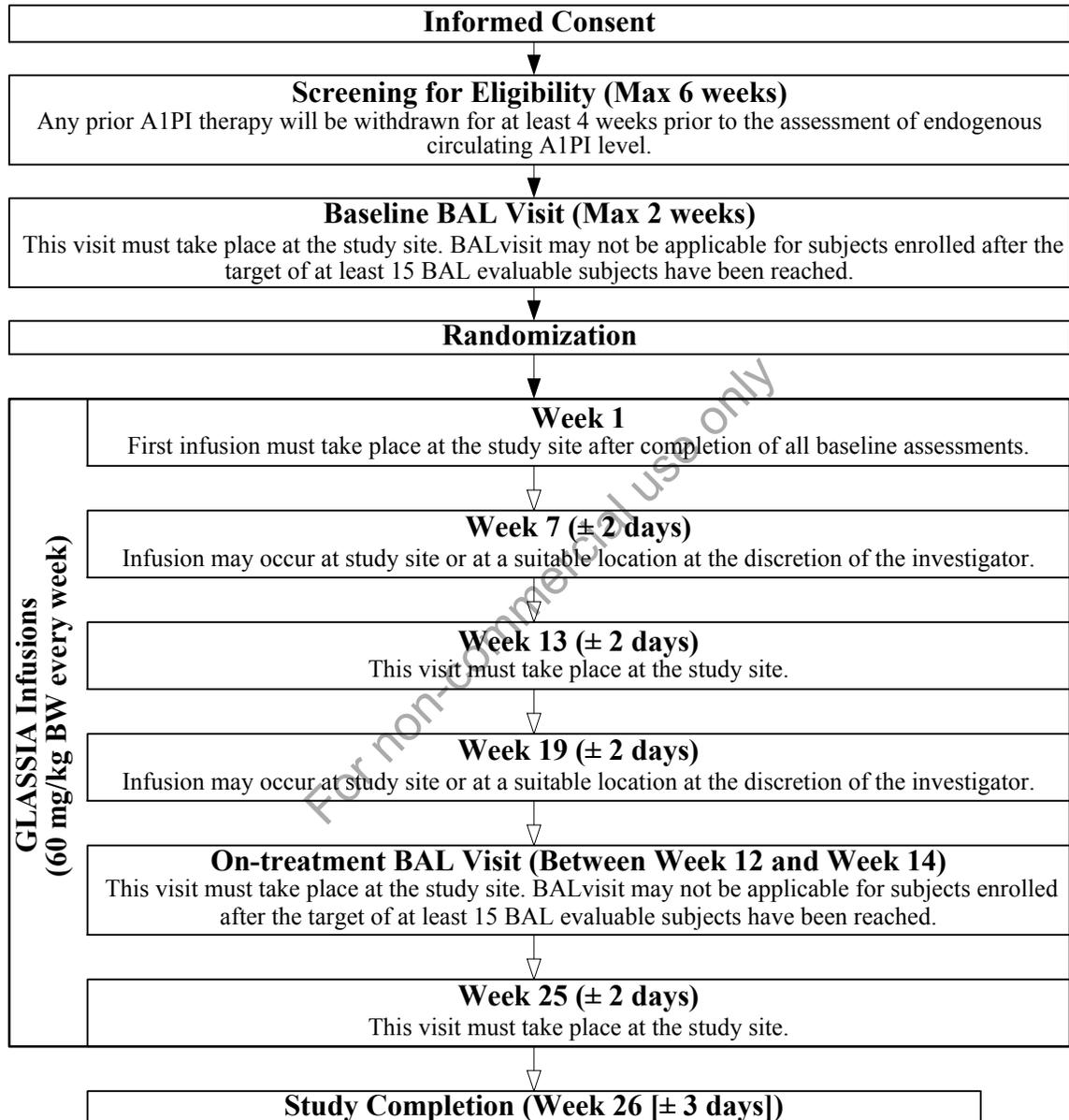
The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 20-1
Study Flow Chart for Baxter Clinical Study 471101



20.2 Schedule of Study Procedures and Assessments

Table 20.2-1 Schedule of Study Procedures and Assessments									
Procedures/ Assessments	Screening (Max 6 Weeks)	Baseline BAL^a (Max 2 Weeks)	Week 1	Week 7 (± 2 Days)	Week 13 (± 2 Days)	On-Treatment BAL (Week 12-14)^b	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination^c
Informed Consent ^d	X								
Eligibility Criteria	X								
Randomization		X ^c							
Demographics	X								
Medical and Medication History	X								
Height	X								
Body Weight ^f	X		X	X	X		X	X	
Physical Exam	X		X ^g		X ^g			X	
Vital Signs	X		X ^h	X ^h	X ^h		X ^h	X ^h	
ECG ⁱ	X								
Chest X-ray/CT ^j	X								
Pulmonary Function Tests ^k	X								
Screening/Safety Laboratory Tests ^l	X		X ^g		X ^g			X ^g	X
Screening/On- Treatment Trough A1PI ^m	X		X ^g	X ^g	X ^g		X ^g	X ^g	X

Table 20.2-1 Schedule of Study Procedures and Assessments									
Procedures/ Assessments	Screening (Max 6 Weeks)	Baseline BAL^a (Max 2 Weeks)	Week 1	Week 7 (± 2 Days)	Week 13 (± 2 Days)	On-Treatment BAL (Week 12-14)^b	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination^c
			X ^g	X ^g	X ^g		X ^g	X ^g	X
Anti-A1PI Antibodies ^{m,n}			X ^g		X ^g			X ^g	X
Weekly GLASSIA Infusions ^o			X —————→						
Adverse Event	X	X	X —————→						X
Concomitant Medications and Non-drug Therapies	X	X	X —————→						X
Telephone Follow- up ^p			X —————→						
Additional Procedures for Subjects Undergoing BAL Procedures									
BAL Procedure		X				X			
Vital Signs		X ^q				X ^q			
BAL and Plasma Urea and A1PI ^m		X				X			
		X				X			

Abbreviations: BAL = Bronchoalveolar lavage; ECG = Electrocardiogram; A1PI = Alpha1-Proteinase Inhibitor.

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- a. For subjects who undergo bronchoscopy/BAL procedures. The baseline bronchoscopy/BAL visit will be postponed once if a subject experiences a moderate or severe COPD exacerbation and/or LRTI during the screening period (see Section 10.4 for more details).
- b. The on-treatment BAL procedure will be performed between Week 12 and Week 14 at least 3 days after the preceding IP infusion but with a minimum of 2 days prior to the next IP infusion. Should a subject miss 1 or more consecutive GLASSIA infusion(s) within 4 week(s) immediately prior to the scheduled on-treatment BAL visit, the BAL procedure will be rescheduled to occur after the subject has received at least 4 consecutive weekly GLASSIA administrations. Additionally, the on-treatment bronchoscopy/BAL visit will be postponed once if a subject experiences a moderate or severe COPD exacerbation and/or LRTI during the screening period (see Section 10.4 for more details).
- c. Subjects who are being discontinued from the study early and having been exposed to IP will be asked to return to the study site 7 ± 3 days after the last infusion for early termination assessments. Subjects who are discontinued early from the study prior to receiving any IP administration will not need to undergo early termination procedures, except for those subjects who have undergone the baseline BAL procedure in which case subjects will be followed for potential post-BAL complications for a period of time in accordance with local institutional standard practice but not to exceed 30 days.
- d. Written informed consent must be obtained prior to performance of any study procedures including screening/re-screening procedures.
- e. Randomization is to take place after verification of subject's meeting all the main eligibility criteria, as well as additional bronchoscopy/BAL-related eligibility criteria (as applicable). For those undergoing bronchoscopy/BAL procedures, randomization is to take place only after the subject has successfully completed the baseline BAL visit with evaluable BAL samples collected.
- f. Body weight will be taken at screening (for the calculation of the initial IP infusion dose [in mg] / volume [in mL]). Body weight will be monitored at 6-week intervals (ie, during Weeks 1, 7, 13, 19, and 25) throughout the study. All body weight measurements must be taken using standardized procedures. Adjustment based on body weight changes during the course of the study is not planned; however, dose (in mg) may be adjusted if deemed medically necessary at the discretion of the investigator (eg, clinically significant body weight changes).
- g. To be performed prior to dosing on the day of the IP administration. Measurements taken prior to the first IP infusion (Week 1) will serve as the baseline values.
- h. During treatment period, vital signs (body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure) are to be taken on the day of IP infusion during Weeks 1, 7, 13, 19, and 25 infusion visits at any time prior to the infusion, at each rate reduction due to AE(s) and/or infusion interruption/discontinuation due to AE(s), and within 90 minutes after the completion of an infusion.
- i. ECG obtained within 26 weeks prior to screening may be used, if available.
- j. Chest X-ray or CT scan obtained within 52 weeks prior to screening may be used, if available.
- k. Pulmonary function tests include spirometry (forced expiratory volume in 1 second [FEV₁] and forced vital capacity [FVC]) and single-breath diffusing capacity of carbon monoxide [DL_{CO}]. Spirometry is to be taken 30 ± 15 minutes after administration of a short-acting inhaled β_2 agonist bronchodilator (eg, 400 μ g of salbutamol, or its equivalent). Measurement of DL_{CO} is to be performed prior to bronchodilator administration and spirometry.
- l. For laboratory assessments, see [Table 20.3-1](#).

- m. Samples will each be split into duplicate aliquots of approximate equal volume. One of the 2 aliquots will serve as the backup sample and stored appropriately until notified by the sponsor.
- n. In the event of suspected immune-related adverse events, unscheduled anti-A1PI antibody samples may be collected as necessary and upon consultation with or notification by the sponsor to support AE investigation. The unscheduled anti-A1PI antibody samples must be accompanied by plasma sample collection for the determination of antigenic and functional A1PI levels.
- o. The first infusion (Week 1), as well as infusions at Week 13 and Week 25, must be administered at the study site. Other weekly infusions may be administered at the study site or at another suitable location (eg, the subject's home) by a qualified healthcare professional, as acceptable per local regulations and standard practices of the study site.
- p. The investigator/designee will contact the subject within 1 business day following 72 hours after the completion of each infusion to document AEs and concomitant medications, as well as non-drug therapies, which may have occurred within 24 and 72 hours after the completion of an infusion.
- q. Vital signs will be measured within 2 hours prior to each BAL procedure and within 1 hour after the completion of the BAL procedure. Pre-BAL vital signs are to be performed prior to the administration of bronchodilator and local anesthesia.

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20.3 Schedule of Clinical Laboratory Assessments

Table 20.3-1 Clinical Laboratory Assessments									
Assessments	Screening (Max 6 Weeks)	Baseline BAL^a (Max 2 Weeks)	Week 1	Week 7 (± 2 Days)	Week 13 (± 2 Days)	On-Treatment BAL (Week 12-14)^b	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination^c
Hematology ^d	W		W ^e		W ^e			W ^e	W
Clinical Chemistry ^f	S		S ^e		S ^e			S ^e	S
Complement Activation and Immune Complex Panel ^g			S ^e		S ^e			S ^e	S
HAV Antibody, HBsAg, HCV Antibody, and HIV-1/HIV-2 Antibody	S								
B19V Serology and NAT ^h			S ^e					S ^e	S
Urinalysis ⁱ	U		U ^e		U ^e			U ^e	U
Pregnancy Test ^j	S/U								S/U
Serum IgA	S								
Serum Cotinine	S				S				S
A1PI Genotype	S								
Screening (Antigenic) A1PI ^{k,l}	P								
On-Treatment Trough Plasma Antigenic A1PI ^l			P ^e	P ^e	P ^e		P ^e	P ^e	P

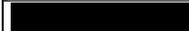
Table 20.3-1 Clinical Laboratory Assessments									
Assessments	Screening (Max 6 Weeks)	Baseline BAL^a (Max 2 Weeks)	Week 1	Week 7 (± 2 Days)	Week 13 (± 2 Days)	On-Treatment BAL (Week 12-14)^b	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination^c
On-Treatment Trough Plasma Functional A1PI ¹			P ^c	P ^c	P ^c		P ^c	P ^c	P
			P ^c	P ^c	P ^c		P ^c	P ^c	P
Serum Anti-A1PI Antibodies ¹			S ^c		S ^c			S ^c	S
Additional Procedures for Subjects Undergoing BAL Procedures									
Plasma Urea ¹		P ^m				P ^m			
Plasma Antigenic A1PI ¹		P ^{m,n}				P ^m			
Plasma Functional A1PI ¹		P ^m				P ^m			
		P ^m				P ^m			
BAL Urea ¹		L				L			
BAL Antigenic A1PI ¹		L				L			
BAL Functional A1PI (ANEC) ¹		L				L			
		L				L			
		L				L			

Table 20.3-1 Clinical Laboratory Assessments									
Assessments	Screening (Max 6 Weeks)	Baseline BAL^a (Max 2 Weeks)	Week 1	Week 7 (± 2 Days)	Week 13 (± 2 Days)	On-Treatment BAL (Week 12-14)^b	Week 19 (± 2 Days)	Week 25 (± 2 Days)	Study Completion (Week 26 ± 3 Days) / Early Termination^c
		L				L			
		L				L			

Abbreviations: BAL = Bronchoalveolar lavage; W = Whole blood; S = Serum; HAV = Hepatitis A Virus; HBsAg = Hepatitis B virus surface antigen; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; NAT = Nucleic acid test; B19V = Parvovirus B19; U = Urine; IgA = Immunoglobulin A; A1PI = Alpha1-Proteinase Inhibitor; P = Plasma; L = Bronchoalveolar lavage fluid; ANEC = Anti-neutrophil elastase capacity; [REDACTED]

- ^a. For subjects undergoing bronchoscopy/BAL procedures.
- ^b. The on-treatment BAL procedure will be performed between Week 12 and Week 14 at least 3 days after the preceding IP infusion but with a minimum of 2 days prior to the next IP infusion. Should a subject miss 1 or more consecutive GLASSIA infusion(s) within 4 week(s) immediately prior to the scheduled on-treatment BAL visit, the BAL procedure will be rescheduled to occur after the subject has received at least 4 consecutive weekly GLASSIA administrations.
- ^c. Subjects who are being discontinued from the study early and having been exposed to IP will be asked to return to the study site 7 ±3 days after the last infusion for early termination assessments. Subjects who are discontinued early from the study prior to receiving any IP administration will not need to undergo early termination procedures, except for those subjects who have undergone the baseline BAL procedure in which case subjects will be followed for potential post-BAL complications for a period of time in accordance with local institutional standard practice but not to exceed 30 days.
- ^d. 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, and neutrophils), absolute neutrophil count (ANC), absolute lymphocyte count, reticulocyte count, and platelet count.
- ^e. Samples must be collected prior to GLASSIA administration.
- ^f. Clinical chemistry panel will consist of sodium, potassium, calcium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactic dehydrogenase (LDH), gamma-glutamyl-transferase (GGT), bilirubin (direct and total), blood urea nitrogen (BUN), uric acid, creatine, creatine phosphokinase (CPK), and glucose.
- ^g. Complement activation and immune complex panel will consist of serum C3, C4, total complement (CH50), C1q binding, and circulating immune complexes.

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- h. Viral testing will consist of viral serology for parvovirus B19 (PVB19) antibody and NAT (PVB19 PCR). If a subject's Week 1 pre-dose sample is tested positive, then no further testing (eg, Week 25) is required.
- i. Urinalysis will consist of color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate, leukocyte esterase, and microscopic examination (RBC, WBC, bacteria, casts).
- j. For females of childbearing potential only. Urine pregnancy test will be performed, unless serum pregnancy test is mandatory as specified by local regulatory/institutional requirements.
- k. For those subjects who are receiving or have recently been exposed to A1PI therapy at the time of study enrollment, pre-study A1PI therapy must be discontinued and sample for the determination of endogenous circulating A1PI level is to be taken after completion of an adequate washout period (approximately 4 half-lives; average half-life ~4.6 days). The screening A1PI measurement may be repeated if an exclusionary level (≥ 8 μM) is obtained that is suspected to be due to inadequate washout of the prior A1PI therapy.
- l. Samples will each be split into duplicate aliquots of approximate equal volume. One of the 2 aliquots will serve as the backup sample and stored appropriately until notified by the sponsor.
- m. Samples must be collected within 2 hours prior to BAL procedure.
- n. For subjects who have received A1PI augmentation therapy prior to study entry, plasma sample for baseline antigenic A1PI level will be collected within 10 days prior to the baseline BAL visit to verify the adequacy of the washout from A1PI therapy prior to performing BAL.

20.4 Thresholds for Clinically Significant Laboratory Abnormalities

Each abnormal laboratory test result will be assessed for clinical significance by the investigator based on the medical judgment of the investigator. Independently, abnormal clinical laboratory values that meet the following criteria will be analyzed and reported.

Laboratory Test	Lowest Alert Limit	Highest Alert Limit	Comment
Hematology			
Hemoglobin (Hgb)	(M) 10.0 g/dL (F) 9.0 g/dL	----	Serial Hgb values allow assessment of the rate of decline over time
Leukocytes	2800/mm ³	16,000/mm ³	To be interpreted in the context of clinical symptoms
Absolute neutrophil count	<1000 /mm ³	---	
Reticulocyte count	<0.5%	>10%	To be interpreted in relation to changes in Hgb and other evidence of bone marrow suppression or hemolysis
Platelet count	<50,000/mm ³	>750,000/mm ³	
Clinical Chemistry			
Sodium	<125 mmol/L	>160 mmol/L	Serial values allow assessment of rate of change
Potassium	<3 mmol/L	>6 mmol/L	To be interpreted in conjunction with possible changes in ECG
ALT	---	>3x ULN	
AST	---	>3x ULN	
ALP	---	>3x ULN	
LDH	---	>3x ULN	
GGT	---	>3x ULN	
Bilirubin (total and indirect)	---	>3x ULN	
Serum creatinine	---	(M) >2.0 mg/dL (F) >1.6 mg/dL	
CPK	---	>5x ULN	
Glucose	<30 mg/dL	>200 mg/dL	Hyperglycemia should be interpreted in the context of known diabetes as a comorbidity
Serum albumin	<3.0 g/dL	----	May indicate protein loss, inflammation or malnutrition
Complement Activation and Immune Complex			
Serum C3	<70 mg/dL	---	
Serum C4	<14 mg/dL	---	
Total complement (CH50)	<30 U/ml	---	
C1q binding	<12 mg/dL		

Laboratory Test	Lowest Alert Limit	Highest Alert Limit	Comment
Urinalysis			
Protein	---	>3+	Must be interpreted in relation to urinary concentration. Only valid when urine specific gravity is ≥ 1.010
RBC	---	>15/hpf or gross hematuria	

Abbreviations: M = Male; F = Female; Hgb = Hemoglobin; ALT = Alanine aminotransferase; ULN = Upper limit of normal; AST = Aspartate aminotransferase; ALP = Alkaline phosphatase; LDH = Lactic dehydrogenase; GGT = Gamma-glutamyl-transferase; CPK = creatine phosphokinase; C3 = Complement component 3; C4 = Complement component 4; CH50 = 50% hemolytic complement activity of serum; RBC = Red blood cell; hpf = High power field.

20.5 Bronchoscopy/Bronchoalveolar Lavage Procedure

Pre-Bronchoscopy:

- Use of anticoagulants such as warfarin or heparin is to be avoided within 7 days prior to and during the BAL procedures.
- It is critical that plasma samples for the measurement of urea, antigenic and functional A1PI levels be collected at the time of the lavage (or shortly before the procedure, not to exceed 2 hours). Plasma urea concentration, assumed to be equivalent to the corresponding urea concentration in the ELF, will be used to estimate the dilution factor in the urea-correction method for the calculation of the ELF analyte levels from the corresponding BAL levels.

Materials:

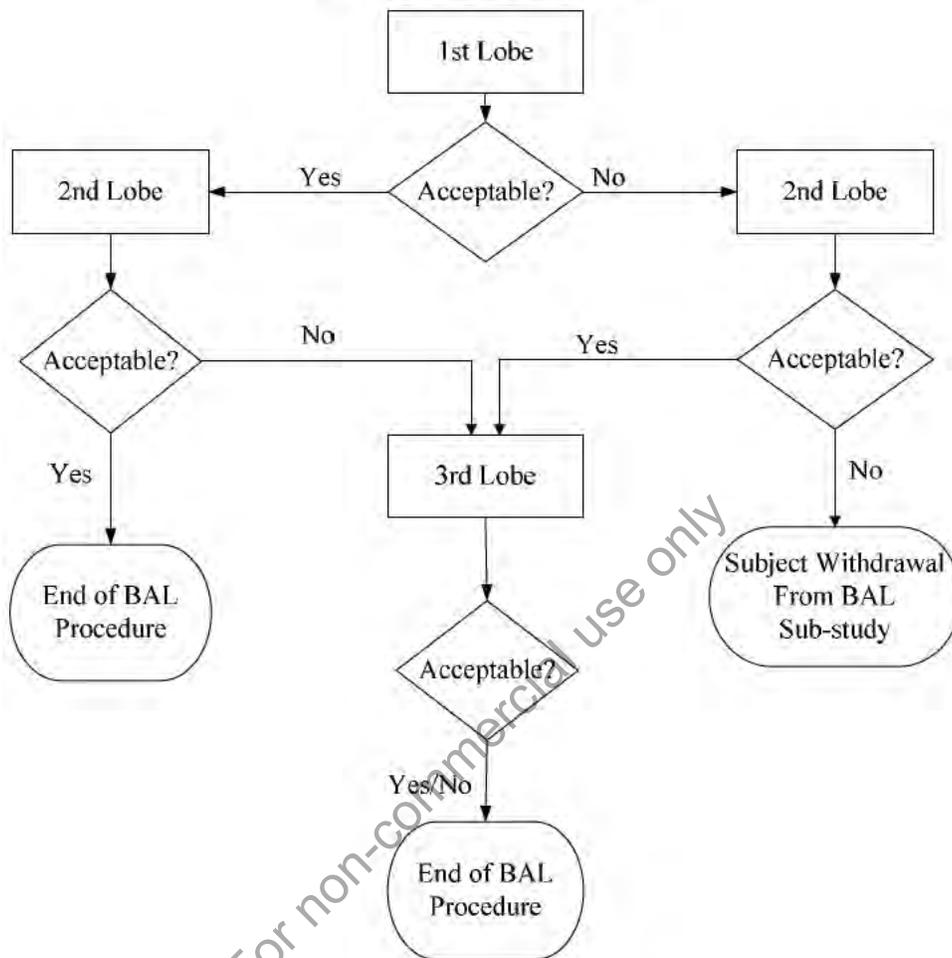
- Continuous suction
- 50 to 100 mL specimen traps
- 50 mL conical tubes
- Sterile normal saline solution
- Bronchoscope
- Sterile cotton gauze
- Centrifuge
- 30 mL syringes for instilling of lavage fluid (5 per lobe)
- 10 to 30 mL syringes for aspirating lavage fluid from specimen traps, as necessary

Procedures:

1. Use local anesthesia, sedation, and pre-medication per standard practice at the local institution. Note: Subject must not have a known history of allergic/hypersensitivity reactions to medications used during and for perioperative care associated with the BAL procedures, such as local anesthetics, sedatives, or pain control medications. Intravenous medication and access to the venous system is typically required for most conscious sedation protocols. The subject should be monitored for ECG, blood pressure, respiratory rate, and pulse oximetry during the procedure. During and after the procedure, the patient should have nasal O₂ at a flow rate sufficient to achieve adequate arterial O₂ saturation. Always bronchodilate the subject prior to local anesthesia.
2. Supine position for bronchoscopy is preferable.
3. Transoral or transnasal intubation, depending on subject's anatomy and comfort, may be required.
4. The right upper lobe anterior segment, right middle lobe medial or lateral segments, and left superior lobe superior or inferior lingular segments generally yield the best lavage returns and are preferred. Avoid bronchiectatic segments. Whenever possible, BAL fluid should be sampled from the same lobes and segments of an individual for both the baseline and the on-treatment BAL procedures.
5. Note any erythema, edema, friability, or secretions. Advance the bronchoscope until the distal lumen fills the airway to a wedge position. (This may be confirmed by gentle suction that causes the collapse of the airway. Take care not to suck too hard to prevent damage to the mucosa.)
6. After adequate administration of conscious sedation and analgesia, the study subject will undergo a fiberoptic bronchoscopy with a BAL in the supine position. Total lavage amount should not exceed 300 mL. The bronchoscope will be wedged initially into 2 lobes (right upper lobe anterior segment, right middle lobe medial or lateral segments, and left superior lobe superior or inferior lingular segments are preferred).

7. Each lobe should be lavaged with 5 sequential 20-mL aliquots for a total of 100 mL per lobe (each syringe should have 5 to 10 mL of air plus saline). The saline should be infused quickly with no dwell time between aspiration and infusion. Control the suction to generate a partial but not complete collapse of the airway; a manual suction or a pump-suction pressure of -80 to 100 cm H₂O is recommended. On the last aliquot, as the return from lobe begins to significantly decrease, have the patient take a deep breath and exhale slowly to collect the remaining return.
8. Process individual BAL aliquots from each lobe separately and immediately after lavage:
 - a. Remove mucus from each sample by pouring the lavage fluid through 2 layers of unfolded sterilized cotton gauze into a 50-mL conical tubes that are placed on ice.
 - b. Spin down the BAL aliquots at approximately 850 x g for 15 minutes to remove cells.
 - c. Harvest the supernatant from each aliquot and discard the pellet.
 - d. For each aliquot, the volume instilled (eg, 20 mL), the volume returned, and the percentage of the original volume that was recovered for each aliquot will be recorded. Returns of less than 20% (ie, <4 mL) or the presence of blood by visual inspection in any individual aliquot will be considered non-evaluable, and the aliquot(s) will be discarded.
 - e. Combine all of the remaining acceptable aliquots (blood-free aliquots with $\geq 20\%$ [ie, ≥ 4 mL] recovery each) for each lobe.
 - f. Calculate and record the overall percentage recovery for each lobe.
 - g. Divide the supernatant in duplicate samples of approximately equal volume and store the samples in a freezer at -70 °C or below until shipment to the central laboratory and until sample analysis.
9. If the overall percent recovery is less than 20% (ie, <20 mL per lobe) or the overall number of acceptable aliquots (blood-free aliquots with $\geq 20\%$ [ie, ≥ 4 mL] recovery each) is less than 3 per lobe for one or both of the lobes, then a third lobe lavage should be attempted (see [Figure 20-2](#)). (In general, for A1PI patients, overall returns are usually 20-50% of total instilled saline.)
10. After a subject completes the study, ship the BAL samples (in duplicates) on dry ice by overnight delivery to the central laboratory. Only evaluable BAL samples will be shipped for sample analyses.

Figure 20-2
BAL Procedural Flow Chart



The following criteria apply to the acceptability of an individual BAL aliquot:

1. Lack of blood in the recovered BAL aliquot based on visual examination; and,
2. A recovered aliquot volume equivalent to $\geq 20\%$ (ie, ≥ 4 mL) of the original instilled volume of saline for each aliquot.

The following criteria apply to the acceptability of a BAL sample pooled from acceptable aliquots for each lobe:

1. Lack of blood in the recovered BAL sample based on visual examination; and
2. A total recovered sample volume equivalent to $\geq 20\%$ (ie, ≥ 20 mL) of the total original instilled volume of saline (ie, ≥ 100 mL); a total of ≥ 3 acceptable aliquots (each blood-free aliquot with ≥ 4 mL) per lobe.

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22. SUMMARY OF CHANGES

Protocol Amendment 1: 2015 JAN 19 **Replaces: Original: 2011 JUL 05**

In this section, changes from the original version of the protocol, dated 2011 JUL 05, 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.
2. Throughout the document
Description of Change: The study design has been revised from a single-arm, open-label study to reflect a 2-arm, double-blind, randomized, controlled study comparing GLASSIA lots with no. of particles of ≥ 2 micron in diameter representing the high end (Treatment Arm 1, 18 planned subjects) vs the low end (Treatment Arm 2, 18 planned subjects) of the range normally observed in GLASSIA lots manufactured.
Purpose for Change: To comply with FDA's request to conduct this post-marketing commitment study as a controlled study.
3. Section 3 Synopsis, Section 6.3 Population To Be Studied, Section 9.1 Inclusion Criteria, Section 9.2 Exclusion Criteria, Section 9.3 Additional Section 9.3 Additional Inclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures, and Section 9.4 Additional Exclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures
Description of Change: The target study population of subjects with severe congenital A1PI deficiency defined on the basis of non-augmented circulating A1PI level and phenotype in the original version of the protocol has been modified to subjects with severe congenital A1PI deficiency defined on the basis

of endogenous A1PI level $<8 \mu\text{M}$ and A1PI genotype. Additionally, subjects must have at least one of the following: clinical diagnosis of emphysema, evidence of emphysema on computerized tomography (CT) scan of the chest within 52 weeks of screening, and/or evidence of airway obstruction which is not completely reversed with bronchodilator treatment at the time of screening (see inclusion criterion #4). Unless being exempted from the bronchoscopy/BAL procedures, subjects must have post-bronchodilator forced expiratory volume in one second (FEV_1) $\geq 50\%$; and, if subject's FEV_1 is $>80\%$ of predicted, then subject must have $\text{FEV}_1/\text{forced vital capacity (FVC)} < 0.7$ and/or DL_{CO} between 30% and 65% predicted at screening. Additional exclusion criteria pertinent to bronchoscopy/BAL procedures have also been included (see item 11 below for detailed descriptions).

Purpose for Change: The subject eligibility criteria have been revised to reflect the intended patient population for which GLASSIA is indicated (ie, subjects with emphysema due to severe congenital deficiency of A1PI), in order to more appropriately evaluate the effects of GLASSIA augmentation therapy on A1PI levels in the target (lung) tissue. In addition, given that bronchoalveolar lavage return tends to be poorer in subjects with severe emphysema, the pulmonary function criterion has been revised to exclude subjects with severe emphysema but to enroll only subjects with mild to moderate emphysema.

4. Section 3 Synopsis, Section 7 Study Purpose and Objectives, Section 8.4 Outcome Measures, Section 13.4 Methods of Analysis, and Section 20.3 Schedule of Clinical Laboratory Assessments

Description of Change: The study objective and outcome measure sections have been re-arranged into primary, secondary, and exploratory categories. The safety outcome measures have been streamlined and re-ordered, such that the primary endpoints would focus on pertinent safety endpoints that are perceived to be associated with protein aggregates or visible/subvisible particles in therapeutic protein products. The immunogenicity endpoint has been revised to "Number (proportion) of subjects who develop binding and/or neutralizing anti-A1PI". The other safety endpoints, such as treatment-emergent AEs, clinically significant shift in laboratory test abnormalities, and B19V seroconversion, are moved to secondary outcome measures. ELF antigenic A1PI level and now with the addition of ELF functional A1PI level serve as primary "efficacy" endpoints of the study, whereas plasma trough antigenic and functional A1PI levels are removed as study endpoints. [REDACTED]

[REDACTED]

Purpose for Change: (i) To re-classify study objectives and outcome measures as primary, secondary, and exploratory in alignment with the sponsor's protocol template. (ii) To consolidate safety outcome measures with improved clarity/readability, and to reflect the hierarchical order of study endpoints by their relevance in accordance with FDA's recommendations. (iii) To specify AEs of interest for the evaluation of possible association of GLASSIA's safety profile to protein aggregates present in GLASSIA solution. (iv) To explicitly state that both binding and inhibitory (neutralizing) anti-A1PI antibodies will be monitored as a safety endpoint of the study. (v) To remove plasma antigenic and functional A1PI levels as study endpoints. (vi) [REDACTED]

5. Section 3 Synopsis, and Section 8 Study Design

Description of Change: Text has been revised to reflect an increase in target BAL evaluable subjects from 12 to at least 15-18, and that *“(s)subjects will be required to undergo bronchoscopy/bronchoalveolar lavage (BAL) procedures at baseline and during augmentation therapy to collect BAL samples for the evaluation of the effects of GLASSIA augmentation therapy on the levels of A1PI and [REDACTED] [REDACTED] in the ELF. Once the target of 15 to 18 evaluable subjects is reached, the remaining subjects to be enrolled will be waived from the baseline and on-treatment bronchoscopy/BAL procedures. ... Enrollment will be closed when both conditions are met.*

- (a) At least 15 evaluable subjects with acceptable BAL samples collected from both the baseline and on-treatment BAL visits have been achieved*
- (b) A minimum of 36 subjects have been randomized.”*

Purpose for Change: The target number of BAL evaluable subjects is increased from 12 to at least 15-18 per FDA's request. The increase in the BAL sample size should in theory increase the power to detect the effect of GLASSIA augmentation therapy in elevating antigenic and functional A1PI levels in the ELF. Based on the past experience from a similar study, it is estimated that approximately 26 to 32 subjects will be needed in order to achieve 15 to 18 BAL evaluable subjects, respectively. Thus, an overall study enrollment target of 36 subjects remains unchanged as this should be adequate to meet the target number of BAL evaluable subjects. If for any reasons the target of at least 15 evaluable subjects have not been attained with the initial 36 randomized subjects, additional subjects will be enrolled to achieve the BAL enrollment target. Text has been added to reflect that both conditions must be met in order for enrollment to be

- considered completed. Additionally, in order to ensure that the BAL enrollment target will be met and given that the majority of the study subjects are expected to be needed, the BAL component of the study has been revised to become an integral part of the study (rather than as an optional sub-study) and that all subjects will be required to undergo bronchoscopy/BAL procedures (unless waived by the sponsor once the target of at least 15 BAL evaluable subjects has been reached).
6. Section 3 Synopsis, Section 8.2 Study Design, Section 8.3 Duration of Study Period(s) and Subject Participation, Section 20.2 Schedule of Study Procedures and Assessments, and Section 20.3 Schedule of Clinical Laboratory Assessments
Description of Change: A separate baseline visit (prior to randomization, with a minimum of 2 days for recovery from bronchoscopy/BAL procedure prior to the first IP infusion) has been specified for subjects undergoing bronchoscopy/BAL procedures. The post-treatment safety follow-up period has been changed from 4 weeks to 1 week, thus the study completion visit is planned to take place during Week 26 (\pm 3 days).
Purpose for Change: To allow adequate time interval for subjects to recover from the BAL procedure prior to the first IP infusion, and to shorten the in-study post-treatment safety follow-up period to 1 week which is adequate and which allows the subjects to be maintained on their own A1PI therapy without much interruption after completing the study.
7. Section 3 Synopsis, Section 8.2 Study Design, Section 10.3.2.1 Preparation and Storage of Pooled IP Solutions, and Section 20.2 Schedule of Study Procedures and Assessments
Description of Change: Revisions have been made to stipulate that subject's body weight is to be measured at 6-weeks intervals (ie, during Weeks 1, 7, 13, 19, and 25. Dose (mg) adjustments due to changes in body weight are not planned, however, dose (mg) may be adjusted if deemed medically necessary at the discretion of the investigator (e.g., clinically significant body weight changes).
Purpose for Change: To add provision for dose (mg) adjustment if deemed medically necessary.

8. Section 3 Synopsis, Section 8.2 Study Design, Section 10.3.2.2 IP Administration, and Section 20.2 Schedule of Study Procedures and Assessments

Description of Change: Revisions have been made to stipulate that GLASSIA infusion is to be administered at the study site during the Week 13 and Week 25 visits.

Purpose for Change: To provide additional safety monitoring and to facilitate prompt AE reporting by requiring additional on-site study product infusions.

9. Section 3 Synopsis, Section 9.1 Inclusion Criteria, Section 9.2 Exclusion Criteria, Section 9.3 Additional Inclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures, and Section 9.4 Additional Exclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures

Description of Change:

Original Protocol	Protocol Amendment 1	Reason for Change
9.1 Inclusion Criteria		
1. Signed and dated informed consent	Deleted	Not applicable; informed consent should have been obtained prior to screening for eligibility.
4. Phenotype Pi Z (which includes Pi*Z/Z, Pi*Z/Null, or Pi*Malton/Z), or Pi*Null/Null	2. A1PI genotype of Pi*Z/Z, Pi*Z/Null, Pi*Malton/Z, or Pi*Null/Null.	To ensure the target A1PI-deficient patients are enrolled.
--	4. Subject must have at least one of the following: clinical diagnosis of emphysema, evidence of emphysema on computerized tomography (CT) scan of the chest within 52 weeks of screening, and/or evidence of airway obstruction which is not completely reversed with bronchodilator treatment at the time of screening.	The subject eligibility criteria has been revised to reflect the intended patient population that GLASSIA is indicated for (ie, subjects with emphysema due to severe congenital deficiency of A1PI) in order to more appropriately evaluate the effects of GLASSIA augmentation therapy on A1PI levels in the target (lung) tissue.

Original Protocol	Protocol Amendment 1	Reason for Change
<p>6. No clinically significant abnormalities (other than emphysema, bronchitis or bronchiectasis) detected on chest X-ray (CXR) at the time of screening (CXR previously obtained within the past 6 months may be used, if available).</p>	<p>6. No clinically significant abnormalities (other than emphysema, and chronic bronchitis) detected on chest X-ray (CXR) at the time of screening (chest X-ray or CT scan obtained within 52 weeks prior to screening may be used, if available).</p>	<p>To clarify that a patient with bronchiectasis will not be eligible. To allow the use of past CT scan of the chest be used for eligibility determination. To increase the time period allowable for the past records of chest x-ray or CT scan from 6 to 12 months.</p>
<p>8. If the subject is treated with any respiratory medications including inhaled bronchodilators, inhaled corticosteroids, or systemic corticosteroids (prednisone \leq 10mg/day or its equivalent), the doses of the subject's medications are unchanged for at least 14 days prior to screening.</p>	<p>7. If the subject is being treated with any respiratory medications including inhaled bronchodilators, inhaled anticholinergics, inhaled corticosteroids, or low-dose systemic corticosteroids (prednisone \leq 10 mg/day or its equivalent), the doses of the subject's medications have remained unchanged for at least 14 days prior to screening</p>	<p>To add inhaled anticholinergics.</p>
<p>7. Laboratory results obtained at the screening visit, meeting the following criteria: a) Serum alanine aminotransferase (ALT) \leq 3 times upper limit of normal (ULN) b) Serum total bilirubin \leq 2 times ULN c) \leq +2 proteinuria on dipstick analysis d) Serum creatinine \leq 2.0 times ULN e) Absolute neutrophil count (ANC) $>$ 1500 cells/μL f) Hemoglobin (Hgb) \geq 9.0 g/dL g) Platelet count \geq 100,000/μL</p>	<p>Under Exclusion Criteria: 12. Abnormal clinical laboratory results obtained at the time of screening meeting the following criteria: a. Serum alanine aminotransferase (ALT) $>$3.0 times upper limit of normal (ULN) b. Serum total bilirubin $>$2.0 times ULN c. $>$2+ proteinuria on urine dipstick analysis d. Serum creatinine $>$2.0 times ULN e. Absolute neutrophil count (ANC) $<$1500 cells/mm^3 f. Hemoglobin (Hgb) $<$9.0 g/dL g. Platelet count $<$100,000/mm^3</p>	<p>This eligibility criterion is moved to Section 9.2 Exclusion Criteria (#12), and to specify proteinuria is to be tested with urine dipstick method.</p>
<p>--</p>	<p>9. The subject is willing and able to comply with the requirements of the protocol.</p>	<p>New criterion added to comply with current protocol standards.</p>

Original Protocol	Protocol Amendment 1	Reason for Change
Section 9.2 Exclusion Criteria		
--	1. The subject is experiencing or has a history of clinically significant pulmonary impairment other than chronic obstructive pulmonary disease (COPD)/emphysema and/or chronic bronchitis.	New exclusion criteria (#1, #2, #6, #7, #9, #10) added to better define target patient population for participation in this study – to exclude conditions that may pose increased risk to the subject’s safety, impede the subject’s ability to comply with the study procedures (eg, BAL), or confound the interpretation of study results.
--	2. The subject is experiencing or has a history of cor pulmonale.	
--	6. The subject has clinically significant congestive heart failure, with New York Heart Association (NYHA) Class III/IV symptoms.	
--	7. The subject is experiencing an active malignancy or has a history of malignancy within 5 years prior to screening, with the exception of the following: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or stable prostate cancer not requiring treatment.	
--	9. The subject is receiving long-term oxygen supplementation (other than on a short-term basis for acute COPD exacerbation, or supplemental O2 with continuous positive airway pressure [CPAP], or bi-level positive airway pressure [BiPAP]).	
--	10. Known history of hypersensitivity following infusions of human blood or blood components.	
--	16. The subject is a family member or employee of the investigator.	New criterion added to comply with current protocol standards.

Original Protocol	Protocol Amendment 1	Reason for Change
<p>Under additional eligibility criteria for the BAL component of the study:</p> <p>3. History of frequent exacerbations (greater than 2 moderate or severe exacerbations in the 12 months preceding the signing of the informed consent</p>	<p>Under exclusion criteria:</p> <p>4. The subject has a history of frequent pulmonary exacerbations (greater than 2 moderate or severe exacerbations within 52 weeks prior to screening).</p>	<p>Original additional exclusion criteria #2 and #3 for BAL sub-study were moved to Section 9.2 as Exclusion criteria #4 and #5. Original additional exclusion criteria #5 for BAL sub-study were moved to Section 9.2 and consolidated with original Exclusion Criterion #5 as the new Exclusion criterion #8, given that these criteria apply to all subjects being screened for study eligibility, not only for BAL sub-study.</p>
<p>2. Presence of clinical symptoms of any lower respiratory tract infection (LRTI) or acute pulmonary exacerbation (APE) within 4 weeks prior to screening</p>	<p>5. The subject is experiencing a pulmonary exacerbation at the time of screening (subject may be re-screened 4 weeks after the clinical resolution of an exacerbation).</p>	
<p>5. History of lung transplant/lung resection</p>	<p>8. The subject has a history of lung or any other organ transplant, is currently on a transplant list, or has undergone major lung surgery.</p>	
<p>Section 9.3 Additional Inclusion Criterion for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures</p>		
<p>Under exclusion criteria: Subjects who meet ANY of the following criteria are not eligible for the BAL component of the study:</p> <p>1. FEV1 < 40% predicted (post bronchodilator)</p>	<p>1. The subject must have pulmonary functions at screening meeting both of the following:</p> <p>a. Post-bronchodilator forced expiratory volume in 1 second (FEV1) ≥50%</p> <p>b. If FEV₁ is >80% predicted, then FEV₁/forced vital capacity (FVC) must be <0.7 and/or DL_{CO} must be ≥30% and ≤65% predicted.</p>	<p>Given that bronchoalveolar lavage return tends to be poorer in subjects with severe emphysema, the qualifying lung functions have been modified to exclude subjects with severe emphysema but to enroll subjects with mild to moderate emphysema.</p>

Original Protocol	Protocol Amendment 1	Reason for Change
Section 9.4 Additional Exclusion Criteria for Subjects Who Are to Undergo Bronchoscopy/BAL Procedures		
<p>Under exclusion criteria: Subjects who meet ANY of the following criteria are not eligible for the BAL component of the study:</p> <p>4. Inability to undergo bronchoscopy (prior history of adverse reaction to local anesthetics, sedatives, pain control medications, and other medications employed at the study site for perioperative care associated with the BAL procedure)</p>	<p>1. The subject has contraindication(s) to bronchoscopy or high risk factors, such as recent myocardial infarction, active myocardial ischemia, other cardiopulmonary instability, tracheal obstruction or stenosis, moderate to severe hypoxemia or any degree of hypercapnia, unstable asthma, uremia, pulmonary hypertension, severe hemorrhagic diathesis, and cervical C1/C2 arthritis.</p>	<p>To add/clarify exclusionary conditions that are contraindications to bronchoscopy and/or may pose increased risk to the subject's safety.</p>
<p>--</p>	<p>3. Known history of allergic/hypersensitivity reactions to medications used during and for perioperative care associated with the BAL procedures, such as local anesthetics, sedatives, pain control medications</p>	
<p>--</p>	<p>4. If the subject is receiving or requires long-term (>4 weeks) immunosuppressive therapy, such as systemic corticosteroids at doses greater than 10 mg/day of prednisone (or its equivalent), mycophenolate mofetil, azathioprine, cyclophosphamide, and rituximab.</p>	

Purpose for Change: See column "Reason for change" in the table above.

10. Section 3 Synopsis and Section 10.4 COPD Exacerbation and Lower Respiratory Tract Infection (LRTI)

Description of Change: The following text has been modified from "*A moderate or severe acute pulmonary exacerbation (APE)* or lower respiratory tract infection (LRTI) occurring within 4 weeks of any of the scheduled BAL visits will result in postponement of the respective visit until any pulmonary exacerbation and/or LRTI symptoms are no longer clinically evident for a minimum of 4 weeks. A moderate or severe acute pulmonary exacerbation or lower respiratory tract infection will not affect the study start or visit schedule of subjects who are not*

enrolled in the BAL substudy.” to “If a subject experiences a moderate or severe COPD exacerbation and/or LRTI during the screening period, baseline BAL visit will be postponed once in order for the subject to recover from the exacerbation (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically evident) and remain stable for at least 4 weeks after the end of exacerbation. If a moderate or severe episode of COPD exacerbation and/or LRTI occurs during the treatment phase, the subject should continue with the planned study visits and to receive weekly infusions of GLASSIA as planned, unless deemed medically inappropriate by the investigator. However, the on-treatment BAL visit will be postponed until clinical resolution of the exacerbation (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically evident) plus an additional minimum period of 4 weeks after the end of exacerbation.” In addition, definitions of onset and end of COPD exacerbation, as well as a diagrammatic presentation illustrating the duration of an episode of COPD exacerbation, are provided in Section 10.4.

Purpose for Change: To clarify that planned study and infusion visits are to be conducted as scheduled during an episode of moderate or severe COPD exacerbation and/or LRTI. The only study procedure that will be postponed due to occurrence of COPD exacerbation is the bronchoscopy/BAL procedure. In this event, subjects must have recovered from the COPD exacerbation and/or LRTI (ie, any signs and symptoms of the COPD exacerbation and/or LRTI are no longer clinically evident) and remained stable (no recurrence of COPD exacerbation and/or LRTI) for at least 4 weeks after the end of the exacerbation.

11. Section 6 Background Information

Description of Change: (i) New paragraphs (5th, 6th, 7th, and 8th) have been added to provide more detailed explanation why this study is being conducted. (ii) The paragraph beginning with “*The primary purpose of this clinical study...*” in the original version of the protocol is revised to align with the primary and secondary goals of this study. (iii) The last paragraph in the original version of the protocol has been deleted, as the information related to the infusion rate of 0.2 mL/kg/min is now available in the GLASSIA package insert (March 2014 version). (iv) New sub-sections have been added: Section 6.1.1 Rationale for the Selection of Dosing Regimen and Section 6.1.2 Rationale for the Selection of Route of Administration and Infusion Rate. (v) Added clinical immunogenicity data from the pivotal Ph II/III study that recently become available.

- Purpose for Change: (i) Added new paragraphs to provide more detailed background information explaining why this study is being conducted. (ii) Made editorial changes to align with the addition of the new paragraphs and to improve readability. (iii) Deleted paragraph to remove outdated information and replace with the appropriate reference. (iv) Added sub-sections to provide the rationale underlying the selected dosing regimen, route of administration, and infusion rate. (v) To provide new safety (immunogenicity) information.
12. Section 6.4 Findings from Nonclinical and Clinical Studies
Description of Change: A new section (Section 6.4 Summary of Nonclinical Data) has been added and all references to IB have been deleted throughout the protocol.
Purpose for Change: Given that the study population is an approved indication for GLASSIA and there is no new clinical and human safety information in GLASSIA IB that is not presented in the package insert (Mar 2014), it is decided that GLASSIA package insert with supplementary information being provided within the study protocol (eg, findings from nonclinical studies) should suffice.
13. Section 8.5 Randomization and Blinding
Description of Change: The text “*This is an open-label, active treatment clinical study.*” is replaced with “*This is a 2-arm, double-blind, randomized, controlled clinical study. In order to minimize/avoid bias, subjects meeting eligibility criteria will be randomly assigned to 1 of 2 treatment arms at a ratio of 1:1 (for those undergoing bronchoscopy/BAL procedures, randomization is to take place only after the subject has successfully completed the baseline BAL visit with evaluable BAL samples collected). Randomization codes will be maintained by an Interactive Response Technology (IRT) via an Interactive Web Response System (IWRS).*”
A new section (Section 8.5.1 Unblinding Procedures at Study Sites) is added.
Purpose for Change: To update the description of the measures taken to avoid/minimize bias, the methods for maintaining randomization codes, and the unblinding procedures.

14. Section 8.7.3 Description of Treatment, Section 10.3.2 Infusion Visits, Section 20.2 Schedule of Study Procedures and Assessments, and Section 20.3 Schedule of Clinical Laboratory Assessments
Description of Change: Infusion visit window has been revised from ± 1 week to ± 2 days. Accordingly, clinic visit window (Weeks 7, 13, 19, 20, and 25) has also been updated to ± 2 days.
Purpose for Change: To ensure that sufficient time is allowed in between two consecutive infusions (ie, no overlapping infusions on the same day or within close temporal proximity).
15. Section 8.8 Source Data
Description of Change: A new section has been added to clearly define Source Data in clinical study protocols.
Purpose for Change: To comply with current protocol standards and ICH GCP requirements.
16. Section 9.5 Withdrawal and Discontinuation
Description of Change: The reasons for withdrawal from study treatment or discontinuation from the study have been updated:
(i) To add further details that include actions to be taken for those events involving subjects who become pregnant or who begin nursing during the study.
(ii) To consolidate and provide additional examples of major protocol deviations that will result in discontinuation from further study treatment or participation.
(iii) To clarify that subjects who do not meet BAL evaluable criteria at the baseline BAL visit will not be randomized and will be discontinued from the study. Subjects who had successfully completed the baseline BAL visit but do not meet BAL evaluable criteria during the on-treatment BAL visit will continue to complete the remaining infusion visits (to collect safety and immunogenicity data) through study completion visit. These subjects will not be counted toward the target of 15 to 18 evaluable subjects, thus additional subjects will need to be enrolled.
Purpose for Change: To improve clarity and to improve the integrity of the study.

17. Section 10.3 Screening and Study Visits

Description of Change: Previous by-study visit sections (Sections 10.3.1 through 10.3.8 in the original version of the protocol) have been deleted and reorganized as follows:

Section 10.3.1 Screening Visit, with sub-sections:

Section 10.3.1.1 Confirmation of Severe Congenital A1PI Deficiency

Section 10.3.1.2 Pulmonary Function Tests

Section 10.3.1.3 Rescreening

Section 10.3.2 Infusion Visits, with sub-sections:

Section 10.3.2.1 IP Administration

Section 10.3.2.3 Management of Treatment-Emergent (S)AEs

Section 10.3.2.4 Pre-Medications

Section 10.3.2.5 Post-Infusion Follow-Up

Section 10.3.3 Clinical Assessment Visits

Section 10.3.4 BAL Visits

Purpose for Change: Section 10.3 has been reorganized to minimize redundancy, since study procedures, study visits, and the timing of assessments have already been provided in tabular form in Section 20.2 Schedule of Study Procedures and Assessments, and Section 20.3 Schedule of Clinical Laboratory Assessments. New sections have been added to highlight important aspects of the study conduct and to provide supplemental information.

18. Section 10.3.1 Screening Visit

Description of Change: Text has been added as follows:

“Additionally, for subjects who are to undergo BAL assessments in the study, randomization is to take place after the subject has met all eligibility criteria (including those listed in Section 9.3 and Section 9.4) and successfully undergone the baseline BAL visit with evaluable BAL samples collected.”

Purpose for Change: To improve clarity regarding the timing of randomization.

19. Section 10.3.2.1 IP Administration

Description of Change: Text has been added to specify alert values for vital signs to be collected during each IP infusion visit that, when met, the investigator should be contacted to determine appropriate action to be taken, as necessary (eg, if prior to infusion, whether the infusion should be administered).

Purpose for Change: To increase the level of safety monitoring by the investigator, given that an infusion may be taken place at a location outside of the study site.

20. Section 10.3.2.2 Management of Treatment-Emergent (S)AEs

Description of Change: The section has been expanded to include measures to be taken, including medical interventions as applicable, reduction of infusion rate and/or interruption/discontinuation of study drug infusions, should the following develop during investigational product administration:

- Severe non-serious AEs or SAEs
- Life-threatening SAEs
- Moderate-to-severe hypersensitivity reactions
- Minor/major rashes

Purpose for Change: To provide specific guidelines for handling infusion associated (S)AEs.

21. Section 10.3.2.4 Post-Infusion Follow-Up, and Section 20.2 Schedule of Study Procedures and Assessments

Description of Change: New study procedure added that requires the investigator/designee to contact the subject at or after 72 hours following each infusion visit via a telephone call.

Purpose for Change: To facilitate the monitoring and recording of adverse events, as well as any changes to the use of concomitant medications and/or non-drug therapies, that occur within 72 hours following each study product administration.

22. Section 10.3.4 BAL Visits, Section 20.2 Schedule of Study Procedures and Assessments, and Section 20.3 Schedule of Clinical Laboratory Assessments

Description of Change: The timing and windows of the baseline and on-treatment BAL procedures have been revised, as follows:

- Baseline bronchoscopy/BAL procedure: A minimum of 2 days prior to the first IP infusion
- On-treatment BAL procedure: between Week 12 to Week 14 with at least 3 days after the last IP infusion but with a minimum of 2 days prior to the next IP infusion

Purpose for Change: To allow subjects sufficient time to recover from the bronchoscopy/BAL procedures prior to the first/next IP infusion.

23. Section 10.3.4 BAL Visits, Section 12.8 Plasma Antigenic and Functional A1PI Levels, and Section 20.3 Schedule of Clinical Laboratory Assessments

Description of Change: The following text has been added:

“For subjects who have received A1PI augmentation therapy prior to study entry, plasma sample for baseline antigenic A1PI level will be collected within 10 days prior to the baseline BAL visit to verify the adequacy of the washout from A1PI therapy prior to performing BAL.”

Purpose for Change: To add repeat measurement of baseline antigenic A1PI level in plasma prior to the baseline BAL visit per FDA request.

24. Section 10.4 COPD Exacerbation and Lower Respiratory Tract Infection (LRTI)

Description of Change: Added the definitions of onset and end of COPD exacerbation, as well as a diagrammatic presentation illustrating the duration of an episode of COPD exacerbation (Figure 10-1).

Purpose for Change: To improve clarity.

25. Section 10.5 Medications and Non-Drug Therapies

Description of Change: (i) In addition to any A1PI augmentation therapy other than IP, the list of prohibited medications has been updated to include: commercially available GLASSIA, and any investigational drug, biologic, or device other than IP that are not permitted at any time during the study. (ii) Immunosuppressive therapies and anticoagulants have been added as medications that are not permitted within 4 weeks and 7 days, respectively, prior to and during the BAL procedures. An exception will be rituximab which is not permitted at any time throughout the study, given the long pharmacokinetic and pharmacodynamic half-life of the biologic. (iii) Text has been added to indicate certain medications (eg, inhaled bronchodilators/anticholinergics/corticosteroids, low-dose systemic corticosteroids, and theophylline) that a subject is taking for a pre-existing medical condition are permitted during the study, provided that stable dosages are to be maintained throughout the study.

Purpose for Change: To provide more detailed information on prohibited and allowed medications.

26. Section 10.6 Subject Completion/Discontinuation, Section 12.7 Clinical Laboratory Parameters, Section 20.2 Schedule of Study Procedures and Assessments, and Section 20.3 Schedule of Clinical Laboratory Assessments
Description of Change: Text has been added to specify that subjects who are discontinued early from the study prior to receiving any IP administration will not need to undergo early termination procedures, except for those subjects who have undergone baseline bronchoscopy/BAL procedure (in which case subjects will be followed for potential post-BAL complications for a period of time in accordance with local institutional standard practice but not to exceed 30 days).
Purpose for Change: To improve clarity related to early termination procedures.
27. Section 10.7 Procedures for Monitoring Subject Compliance
Description of Change: Added trough antigenic and functional A1PI in plasma as a measure of subject's compliance/adherence to treatment.
Purpose for Change: To state the purpose behind sample collection and analysis for plasma A1PI levels.
28. Section 11 Assessments of Efficacy
Description of Change: Section 11.1 Plasma Antigenic and Functional A1PI Levels in the original version of the protocol has been deleted.
Purpose for Change: To be consistent with the removal of plasma antigenic and functional A1PI levels as efficacy outcome measures.
29. Section 11 Assessments of Efficacy
Description of Change: Detailed BAL procedures outlined in Section 11.2 Antigenic and Functional A1PI in the ELF, including the BAL Procedural Flow Chart, in the original version of the protocol has been moved to Section 20.5 Bronchoscopy/Bronchoalveolar Lavage Procedure.
Purpose for Change: To improve readability.
30. Section 11.2 [REDACTED]
Description of Change: Added new section.
Purpose for Change: Section inadvertently omitted in the previous version of the protocol.

31. Section 12.1.1.1 Serious Adverse Event

Description of Change: The following text has been added:

“Uncomplicated pregnancies, following maternal or paternal exposure to the 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.”

Purpose for Change: To comply with current protocol standards.

32. Section 12.1.1.3 Adverse Reactions Plus Suspected Adverse Reactions

Description of Change: A new section has been added to provide definition of adverse reactions, as follows:

“An AR plus suspected AR 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 ARs 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.”

Purpose for Change: To provide definition of adverse reactions for safety analysis in accordance with FDA’s request.

33. Section 12.1.1.4 Unexpected Adverse Events

Description of Change: The following text has been added:

“Any AEs (expected and unexpected) will be recorded on the AE CRF.”

Purpose for Change: To improve clarity.

34. Section 12.1.1.5 Adverse Events Potentially Associated with Protein Aggregates
Description of Change: New section added to indicate that the safety data collected in this study will be reviewed and assessed for potential association with protein aggregates in the GLASSIA solution. Listing of AEs of interest by treatment arm will be provided in the clinical study report. Examples of potential AEs of interest were removed from safety endpoint section.
Purpose for Change: To improve readability.
35. Section 12.2 Urgent Safety Measures
Description of Change: A new section has been added.
Purpose for Change: To explicitly define and provide examples of urgent safety measures that should be taken immediately with or without prior authorization from the sponsor in order to protect subjects against immediate hazard to their health or safety.
36. Section 12.3 Untoward Medical Occurrences
Description of Change: The following text has been added:
“For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) (eg, washout of a subject’s pre-study A1PI augmentation therapy, bronchoscopy/BAL procedures) will be recorded on the AE CRF. These events, if occurred before the first IP exposure, will not be considered as AEs and will not be included in the analysis of AEs. On the other hand, these events, if occurred after initiation of IP treatment, will be considered as AEs and will be included in the analysis of AEs.”
Purpose for Change: To make a revision such that procedure-related untoward medical occurrences, whether expected or unexpected, will all be captured and analyzed as AEs if occurring after IP exposure.
37. Section 12.4 Non-Medical Complaints
Description of Change: A new section has been added.
Purpose for Change: To comply with current protocol standards, and to specify a requirement for the site to report any non-medical complaints.
38. Section 12.7.1 Hematology and Clinical Chemistry, Section 12.7.2 Complement Activation and Immune Complex Panel, Section 12.7.3 Viral Serology and Nucleic Acid Tests, Section 12.7.4 Urine Tests, Section 12.8 Plasma Antigenic and Functional A1PI Levels, Section 12.9 Immunogenicity, Section 20.2 Schedule of Study Procedures and Assessment, and Section 20.3 Schedule of Clinical Laboratory Assessments

Description of Change: The following time points have been modified to clinical laboratory assessments:

For all subjects:

- (a) Hematology, Clinical Chemistry, Urinalysis – Added to Week 26 (study completion visit)
- (b) Complement Activation and Immune Complex Panel – Deleted from screening visit (as this is not part of eligibility determination), and added to Week 26 (study completion visit).
- (c) Viral testing for HAV, HBV, HCV, and HIV-1/2 - Only serology testing will be performed and only at screening to support eligibility determination; NAT at baseline and study completion/early termination are no longer required per FDA's communication.
- (d) Viral testing for B19V – Both viral serology and NAT will be performed. Instead of screening, baseline B19V viral testing will be performed prior to the first IP infusion during Week 1, prior to the last infusion during Week 25, and at study completion/early termination.
- (e) Serum anti-A1PI antibodies– Added to the Week 13 and Week 25 visits
- (f) Pregnancy test – Clarified that, while urine pregnancy test will be the default test to be performed, serum pregnancy test may be performed if specified by local regulatory/institutional requirements.

For those subjects undergoing bronchoscopy/BAL procedures:

- (a) Plasma antigenic and functional A1PI – Added to baseline and on-treatment BAL visits to be collected at the same time as plasma urea samples
- (b) [REDACTED]

Purpose for Change: To enhance the ability to detect and/or evaluate treatment-emergent incidences of immunogenicity, hypersensitivity reactions, or other potentially immune-mediated AEs, if any, that may be associated with residual protein aggregates present in GLASSIA infusion solution despite the use of a 5-micron inline filter, and to better characterize the time course of such events by stipulating clinical laboratory assessments at baseline, at 3-month intervals during treatment, and after a 1-week post-treatment safety follow-up period.

39. Section 12.7.6 Biobanking

Description of Change: A new section has been added to explicitly state that plasma samples for A1PI and urea, serum samples for anti-A1PI antibodies, and BAL samples for antigenic and functional A1PI, urea as well as other [REDACTED] [REDACTED] should be divided and stored as duplicate aliquots, such that one of the aliquots will serve as back up samples.

Purpose for Change: To ensure back up aliquots will be collected.

40. Section 12.10 Vital Signs

Description of Change: The frequency of infusion visit vital sign measurements has been adjusted from “...at screening and within 30 minutes before and after ... each administration of IP and at each study visit.” to “ at screening, during treatment period (Weeks 1, 7, 13, 19, and 25), and at study completion (Week 26)/early termination visit. ... For each of the IP infusion visits where vital signs are to be taken, vital signs will be recorded at any time prior to the start of an infusion, at each rate reduction due to AE(s) and/or infusion interruption/discontinuation due to AE(s), and within 90 minutes after the completion of an infusion.”

Purpose for Change: To reduce the burden on site, infusion nurse, and subject, given that GLASSIA is safe and well tolerated even at the higher infusion rate of 0.2 mL/kg/min.

41. Section 3 Synopsis, and Section 13.1 Sample Size and Power Calculations

Description of Change: Text has been revised to the following:

“Using this variance estimate, a sample size of 15 evaluable subjects should be sufficient to detect a mean difference in the natural log transformed ELF antigenic A1PI of approximately 0.87 with 90% power, using a paired t-test and a one-sided significance level of 0.025.”

Additionally, similar sample size and power calculations have been performed based on functional A1PI levels in ELF, as follows:

“A sample size of 15 evaluable subjects will also be sufficient to detect a mean difference in the natural log transformed ELF functional A1PI (ANEC) of approximately 1.04, with 90% power, assuming a standard deviation in the differences between pre- and post-treatment ANEC values to be 20% higher than that for antigenic A1PI.”

Purpose for Change: (i) To update power calculations on the basis of change from baseline in ELF antigenic A1PI levels, in light of the increase in BAL target from 12 to 15 evaluable subjects. This increase in the number of BAL evaluable subjects should have 90% power to detect a smaller treatment effect (a mean treatment difference from approximately 1.0 to 0.87). (ii) To add power calculations for ELF functional A1PI level, which is considered to be a key ELF analyte.

42. Section 13.2 Datasets and Analysis Cohorts

Description of Change: Definition of full analysis set has been revised to replace "... have at least one available measurement for at least one efficacy variable" to "...have at least one available A1PI measurement during the treatment period" (Section 13.2.1). Definition of per-protocol analysis set has been modified to add a total of >15 missed planned infusions will be considered as a major protocol deviation for the purpose of statistical analysis and the subject will be excluded from the per-protocol analysis (Section 13.2.2). Definition of BAL analysis set has been revised to reflect that subjects who missed 1 or more infusions within 4 weeks immediately preceding the scheduled on-treatment bronchoscopy/BAL procedure would be excluded from BAL analysis dataset.

Purpose for Change: To update statistical analysis dataset definitions.

43. Section 13.4 Methods of Analysis

Description of Change: Editorial changes have been made to Section 13.4.1 Efficacy Outcome Measures and Section 13.4.3 Safety Outcome Measures. A new section (Section 13.4.2 Exposure) is added. Analysis of adverse reactions has been added. In addition, the following text has been added:

"AEs that are considered potentially related to the presence of protein aggregates or immune-mediated will be summarized descriptively with 95% confidence intervals (CIs) as appropriate for each AE of interest by each treatment arm and, if appropriate, pooled across both treatment arms. In the event of any clinically significant trends in treatment-emergent AE(s) of interest, further analysis including potential correlation with the presence of particulates in the GLASSIA solution will be performed."

“The proportion of subjects who develop binding and/or neutralizing anti-A1PI antibodies will be summarized with their point estimates and exact 95% CIs. Treatment-emergent anti-A1PI antibody data will be listed along with the corresponding plasma antigenic and functional A1PI levels in the individual subject. Additionally, temporal relationship of anti-A1PI antibody formation with potentially immune-related AEs, if any, will be examined.”

Purpose for Change: To improve clarity, to add safety analysis for adverse reactions, to add provision for analyzing the possible relationship between specific types of AEs and the potential presence of particulates in GLASSIA, and to add provision for analyzing the temporal association of the appearance and presence of treatment-emergent serum antibodies against A1-PI with occurrence of adverse events which may be immune-mediated.

44. Section 3 Synopsis, and Section 13.4.1 Efficacy Outcome Measures

Description of Change: The following text has been added:

[REDACTED]

Changes from baseline in ELF and plasma antigenic and functional A1PI levels, as well as [REDACTED], will be summarized in the following subgroups: by sex, age (≤ 65 , > 65), race, and ethnicity. [REDACTED]

[REDACTED]

Purpose of Change: [REDACTED]

45. Section 3 Synopsis, and Section 13.4.3 Safety Outcome Measures

Description of Change: The following text has been added:

“Safety parameters will be summarized descriptively by sex, age (≤ 65 , > 65), race, and ethnicity. No hypothesis tests are planned, however, [REDACTED]

[REDACTED]

Purpose of Change: To add descriptive analysis of safety data by subgroups per FDA’s request.

46. Section 15.1.1 Investigator Report and Final Clinical Study Report (in the original version of the protocol)
Description of Change: This section has been deleted.
Purpose for Change: This section is not applicable, as the study is not planned to be conducted in the European Union.
47. Section 15.5 Non-Compliance with the Protocol
Description of Change: The following text has been modified (Strikethrough text denotes deleted text, and underlined text denotes added text):
“*The investigator may deviate from the protocol **only** to eliminate an apparent immediate hazard to the ~~subject or when the change(s) involves only logistical or administrative aspects of the study (eg, change of study monitor, change of phone number)~~. 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 ~~5 working days~~ **1 calendar day** after the change is implemented. ~~The investigator~~ **sponsor** will also notify the EC of the emergency change **ensure the responsible ethics committee is notified of the urgent measures taken in such cases according to local regulations.**”
Purpose for Change: To comply with current protocol standards and regulatory requirements.*
48. Section 16.3 Informed Consent
Description of Change: The sentence “*An assent form may be provided and should be signed by patients less than 18 years of age.*” has been deleted.
Purpose for Change: Not applicable, since this study will enroll only adult subjects with A1PI deficiency and emphysema.
49. Section 20.4 Thresholds for Clinically Significant Laboratory Abnormalities
Description of Change: A new section added to provide a table of relevant clinical laboratory test threshold values which are considered significant, independent of the medical assessment made by the investigator, for reporting and safety analysis.
Purpose for Change: Per FDA’s request.

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: GLASSIA

STUDY TITLE: A Phase 4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha₁-Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects

PROTOCOL IDENTIFIER: 471101

CLINICAL TRIAL PHASE 4

AMENDMENT 1: 2015 JAN 19

Replaces Original: 2011 JUL 05

ALL VERSIONS:

Amendment 1: 2015 JAN 19

Original: 2011 JUL 05

OTHER ID(s)

NCT Number: Not Available

EudraCT Number: Not Available

IND NUMBER: 14774

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, 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 Principal Investigator

Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT
PRODUCT: GLASSIA

STUDY TITLE: A Phase 4 Study to Evaluate the Safety, Immunogenicity, and Effects on the Alpha₁-Proteinase Inhibitor (A1PI) Levels in Epithelial Lining Fluid Following GLASSIA Therapy in A1PI-Deficient Subjects

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Signature of Coordinating Investigator

Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative

Date

██████████, MD

██████████, Clinical Development